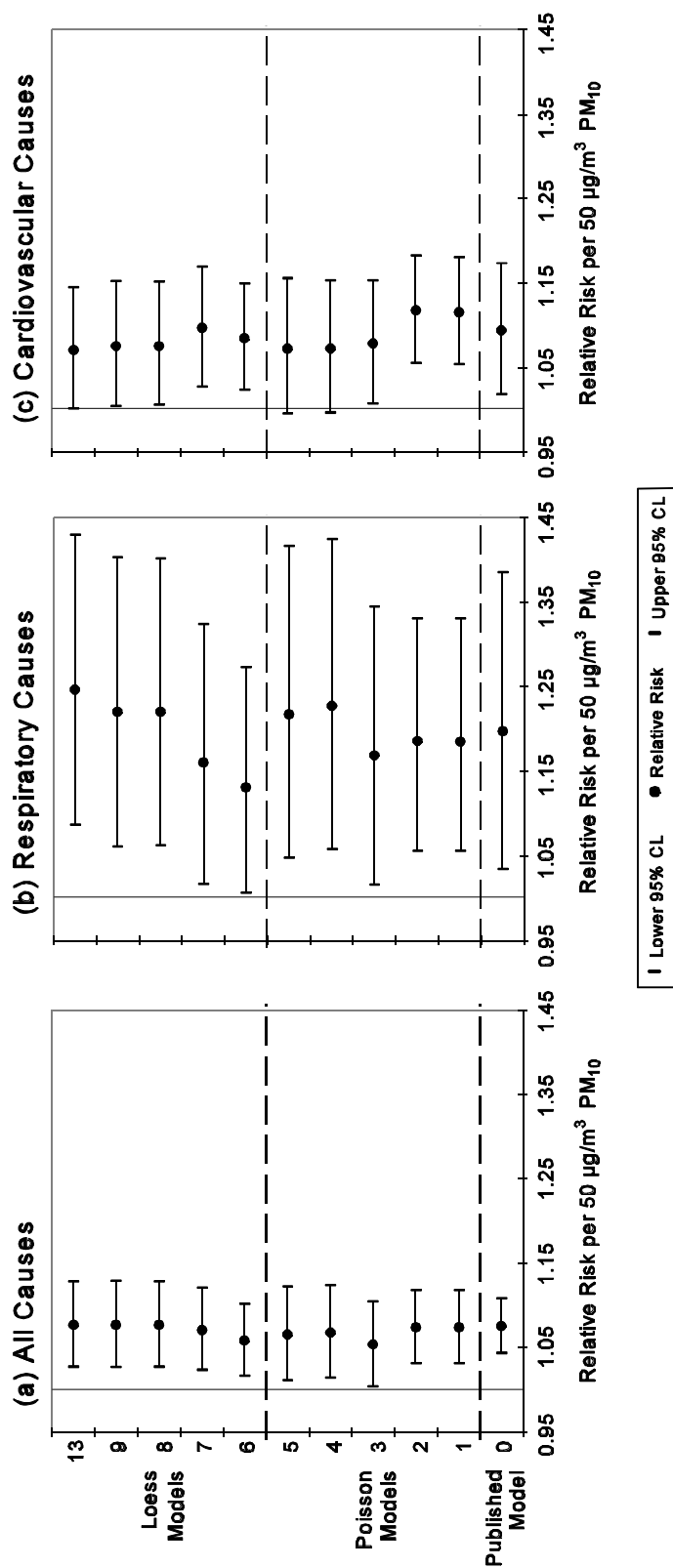


### ***Model Specification for the Utah Valley Mortality Study (Pope et al., 1992)***

One of the most comprehensive assessments of alternative model specifications was presented by Pope in a report presented at the EPA-sponsored workshop on PM-related mortality held in November, 1994 (Pope, 1994). The results of these additional analyses of the Utah Valley study were described briefly in Section 12.3.1 and are presented below graphically, with a view towards resolving model specification issues. For each comparison, a sequence of three graphs is presented that illustrates the results for total (non-accidental) mortality, for death from respiratory causes, and for death from cardiovascular causes. The horizontal bars show the 95 percent confidence limits for relative risk (denoted RR) corresponding to  $50 \mu\text{g}/\text{m}^3$  in  $\text{PM}_{10}$ .

Figures 12-18a through 12-18c show the RR estimates for Poisson regression models. The RR for PM quintiles given in the published paper (Pope et al., 1992) is denoted Model 0. The next group, Models 1 through 5, show the results of fitting increasingly adjusted parametric models, from those with only a linear  $\text{PM}_{10}$  effect (Model 1), and subsequently adding adjustments for time trend (Model 2), temperature (Model 3), humidity (Model 4), and operation of the mill (Model 5) to the preceding model. The relative risk for total mortality (Figure 12-18a) was little affected in Models 1 and 2, but dropped somewhat after temperature was included (Model 3). The relative risk for respiratory mortality (Figure 12-18b) was less affected by temperature, but shifted upward after humidity was added (Model 4). Cardiovascular mortality (Figure 12-18c), like total mortality, also dropped slightly after temperature was added to the model. The relative risk for the next four models (Model 6 through 9) are parallel to Models 2 through 5, except that a non-parametric smoothing function LOESS was used to model time trend, temperature, and humidity respectively in Models 6, 7, and 8; a dummy variable for mill operation was added in Model 9. Model 13 is the same as Model 8 without adjusting for time trend by a LOESS fit on day of the study. In general, RR using at least one LOESS smoother provided a somewhat higher RR for total mortality against  $\text{PM}_{10}$  in the Utah Valley study, but the difference in RR among these Poisson models is small. RR for respiratory mortality increased as each smoothed covariate was added, but never rose much beyond that for the published model. LOESS smoothers had little effect on RR for cardiovascular mortality.



**Figure 12-18. Relative risk of mortality for PM<sub>10</sub> in Utah Valley, as a function of several parametric and semiparametric models of time, temperature, and dewpoint: (a) all causes, (b) respiratory causes, and (c) cardiovascular causes.**

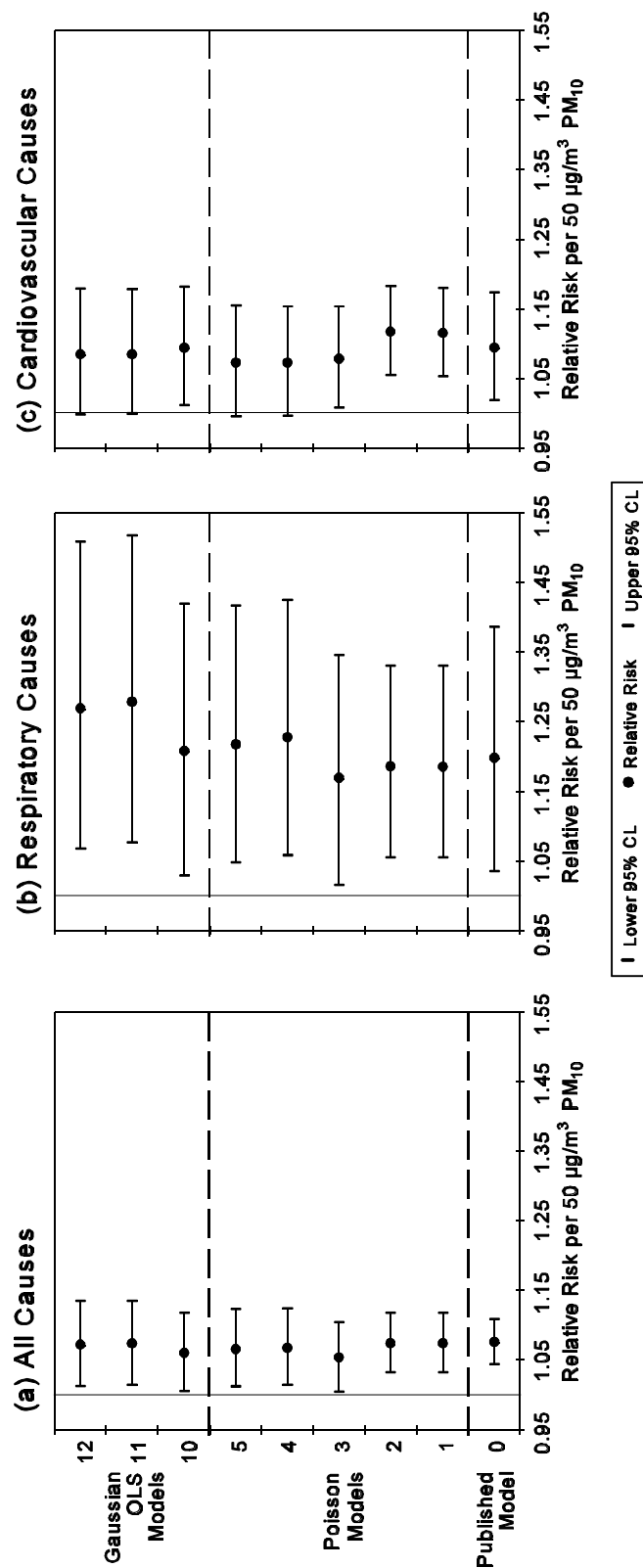
Source: U.S. EPA graphical depiction of results from Pope et al. (1992) and Pope (1994).

The next group of model comparisons is shown as Figures 12-19a through 12-19c. These compare several parametric Poisson models with the analogous Gaussian ordinary least squares (OLS) linear models for mortality. Even though the distributional assumptions for a Gaussian distribution fail utterly, the regression coefficients and calculated RR are not very different than the analogous estimates from Poisson regression models.

Figures 12-20a through 12-20c show the effects of separating the annual data into segments, here called "summer" (April to September) and "winter" (October to March). The RR for total mortality (Figure 12-20a), for respiratory mortality (Figure 12-20b), and for cardiovascular mortality (Figure 12-20c) are all statistically significant on an annual basis, while differing substantially in magnitude. Most of this effect is seen to occur from the winter months when the  $PM_{10}$  concentrations were highest, whether or not the mill was operating, based on Model 13 in which temperature and humidity effects were adjusted using LOESS smoothing. The relative risk and its estimated uncertainty for all three mortality endpoints is nearly the same using whole year data as when using winter data alone. While PM levels are generally much lower during the summer half of the year than in the winter half, the summer RR estimates are higher than the winter RR estimates, but not significantly different. However, the smaller range of summer PM values results in much larger uncertainty about the summer RR than the winter RR. This illustrates a general problem in subsetting the data by year, season, or month: the increased specificity of RR estimates for subsets of data is usually offset by the loss of precision in the estimates. In general, small increases in uncertainty of subset data RR estimates compared to whole data set RR estimates occur only for the subset(s) of the data that are most influential in establishing the whole data set RR estimate, such as the "winter" subset in this Utah Valley study.

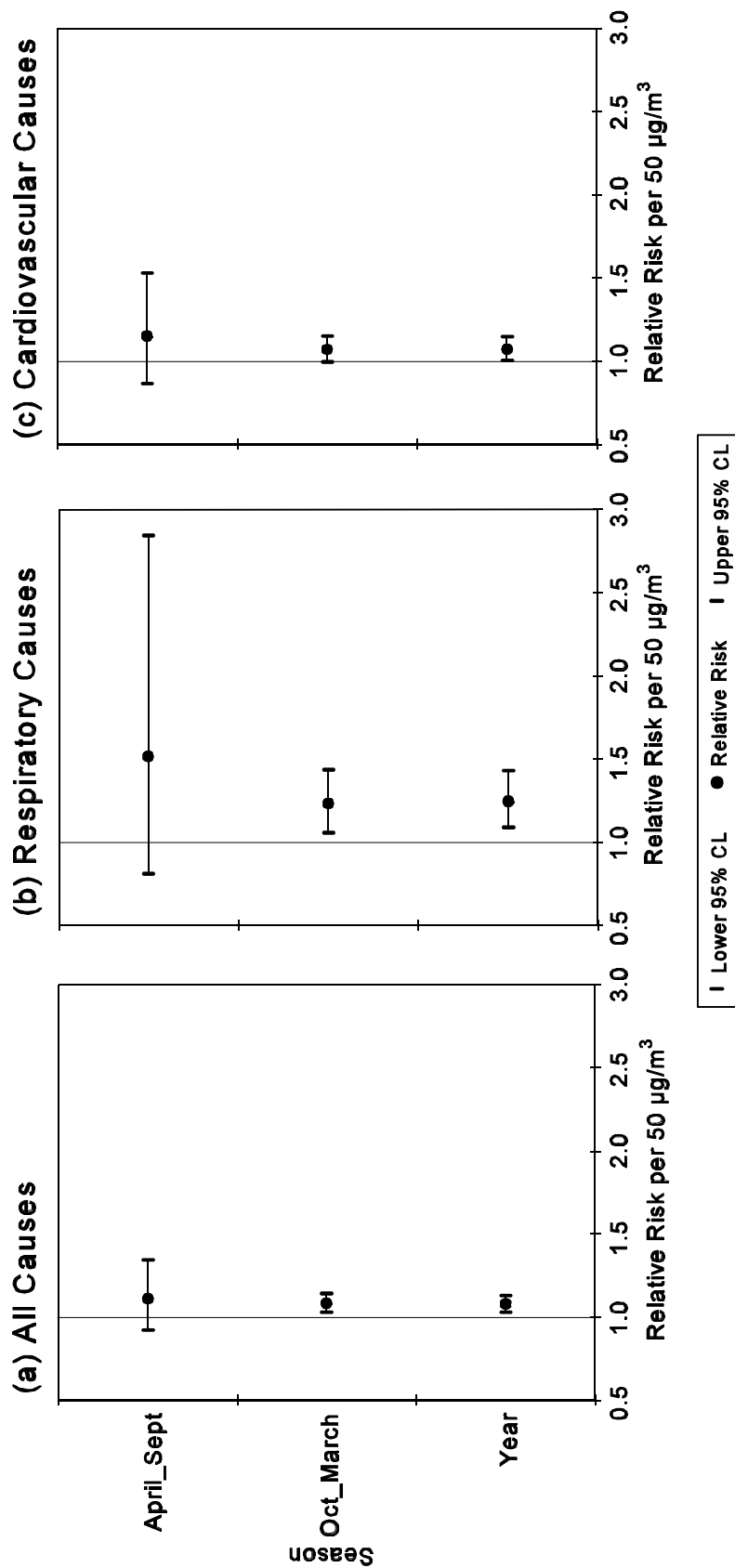
A number of additional reanalyses have recently been presented by Pope and Kalkstein (1996) with results that are almost identical to those shown here. These results demonstrate the relative lack of sensitivity to other methods for weather adjustments, including use of synoptic climatologic categories.

Figures 12-21a through 12-21c extend these Utah analyses to assessing the effect of a co-pollutant, ozone. Including either daily average ozone concentration or maximum one-hour  $O_3$  concentration as predictors of the three mortality endpoints leaves the  $PM_{10}$  RR



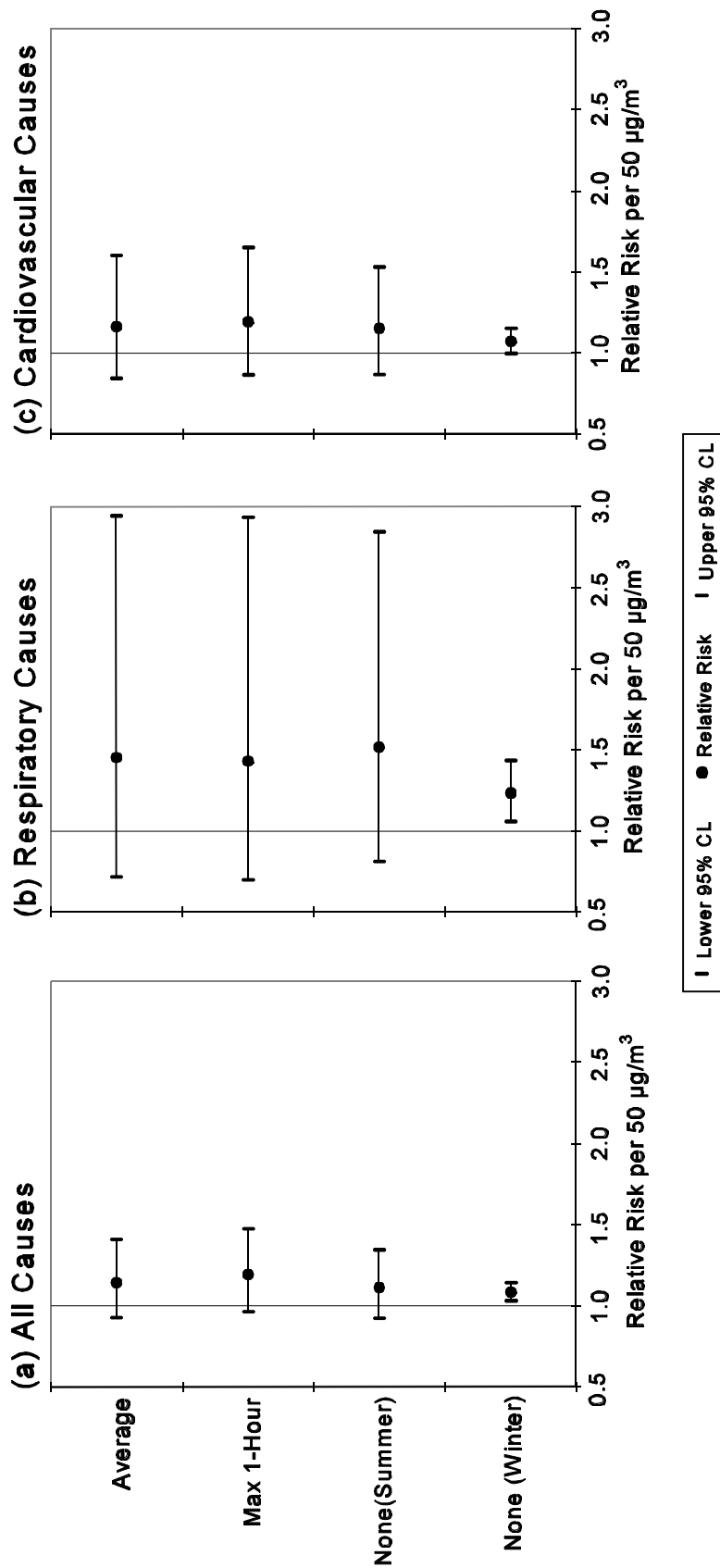
**Figure 12-19. Relative risk of mortality for PM<sub>10</sub> in Utah Valley, as a function of several Poisson and Gaussian regression models of time, temperature and dewpoint: (a) all causes, (b) respiratory causes, and (c) cardiovascular causes.**

Source: U.S. EPA graphical depiction of results from Pope et al. (1992) and Pope (1994).



**Figure 12-20. Relative risk of mortality for PM in Utah Valley, as a function of season: (a) all causes, (b) respiratory causes, and (c) cardiovascular causes.**

Source: U.S. EPA graphical depiction of results from Pope et al. (1992) and Pope (1994).



**Figure 12-21. Relative risk of mortality for PM in Utah Valley, as a function of ozone indicator in the model: (a) all causes, (b) respiratory causes, and (c) cardiovascular causes.**

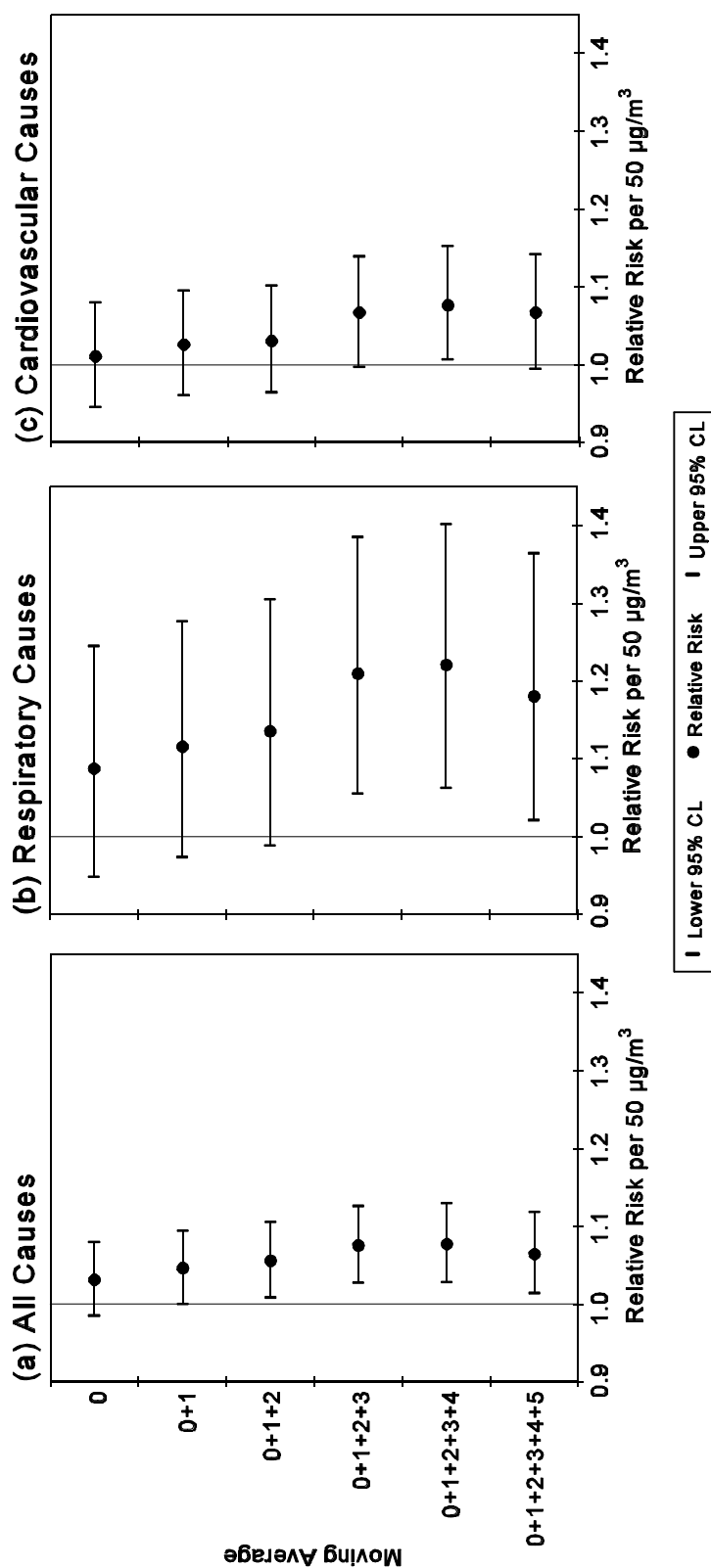
Source: U.S. EPA graphical depiction of results from Pope et al. (1992) and Pope (1994).

estimate nearly unchanged from the summer  $PM_{10}$  RR estimate obtained without including  $O_3$  as a predictor. Summer RR estimates for all models, with or without  $O_3$ , are somewhat larger than the winter or whole-year RR estimate for PM, and have much greater uncertainty. It may be argued that this indicates little confounding of the estimated PM effect with an estimated  $O_3$  effect, and by implication little potential for confounding with other pollutants generated by combustion of fossil fuels by mobile sources, at least in this study.

Figures 12-22a through 12-22c show that specification of PM averaging time may be a critical component of the modelling exercise. Moving averages of 4, 5, or 6 days would provide very similar estimates of a statistically significant PM effect on total mortality (Figure 12-22a) or respiratory mortality (Figure 12-22b). The 5-day moving average used by Pope in most analyses gave the better prediction of cardiovascular mortality (Figure 12-22c).

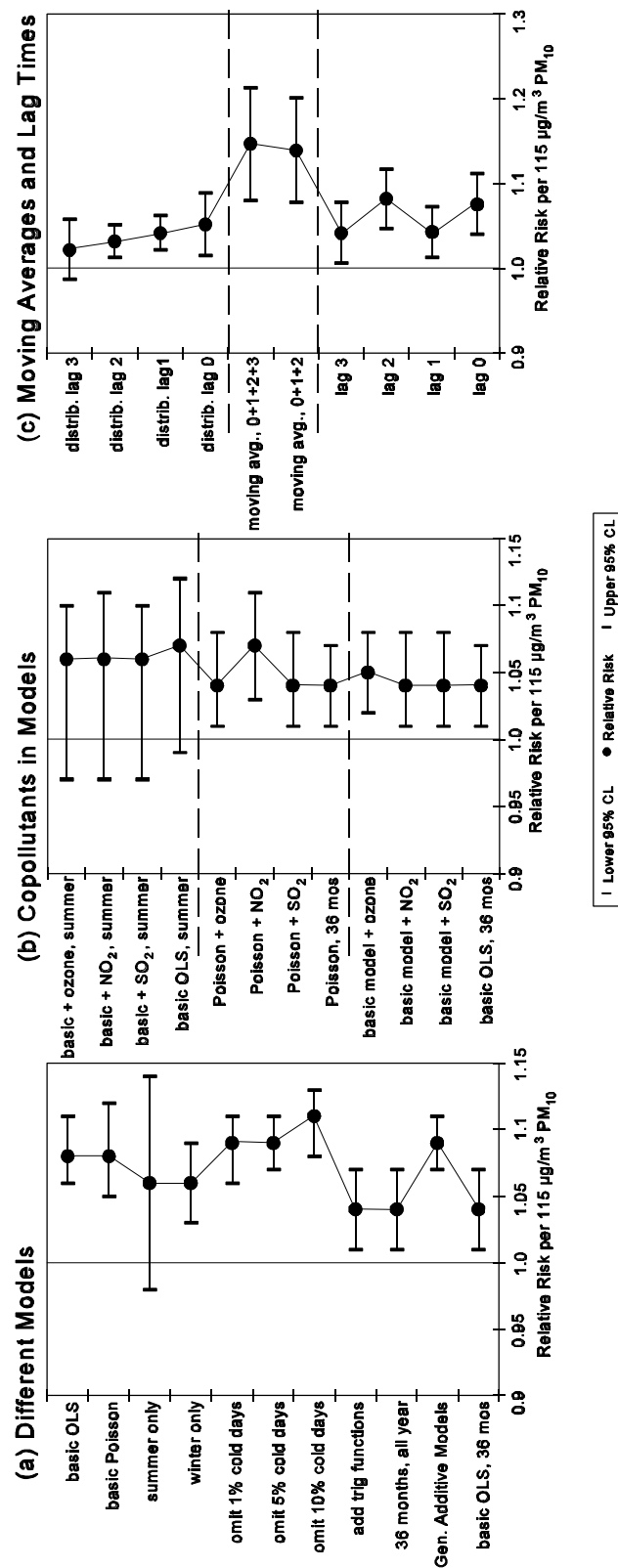
### ***Model Specification for the Santiago, Chile, Mortality Study (Ostro et al., 1996)***

Many model specifications were evaluated in the study by Ostro et al. (1996) discussed in Section 12.3.1. Model specification tests were designed to systematically examine important issues, and results were reported in detail. Figure 12-23 depicts the results graphically. Figure 12-23a shows the RR estimates and large-sample confidence intervals for 10 different Poisson regression models. Figure 12-23a shows the RR values in Table 3 of the Ostro et al. (1996) paper calculated to a base of  $115 \mu g/m^3$  for models that are linear in average or maximum  $PM_{10}$ , or for a change from 115 to  $230 \mu g/m^3$  for their logarithms. Inclusion of temperature-related variables reduced RR slightly, from about 1.16 to about 1.10. Inclusion of additional dummy variables for year, quarter, and day of week had little effect on RR, but adding variables for quarter and month reduced RR to about 1.05, which was still statistically significant. Figure 12-23a also shows the results of additional sensitivity tests controlling seasonality in a variety of different ways. The results are somewhat parallel to those of the Utah Valley study discussed above, but with somewhat smaller values. Summer and winter coefficients were very similar, but the RR effect was not quite statistically significant in summer using a two-tailed test with  $\alpha = 0.05$ . All other model specifications showed a significant  $PM_{10}$  effect. The RR of the effect increased somewhat



**Figure 12-22. Relative risk of mortality for PM in Utah Valley, as a function of the moving average model: (a) all causes, (b) respiratory causes, and (c) cardiovascular causes.**

Source: U.S. EPA graphical depiction of results from Pope et al. (1992) and Pope (1994).



**Figure 12-23. Relative risk of total mortality for PM<sub>10</sub> in Santiago, Chile, as a function of (a) different models, (b) models for copollutants, and (c) moving averages and lag times.**

Source: U.S. EPA graphical depiction of results from Ostro et al. (1996).

when the coldest days were omitted. Including additional trigonometric terms, or including 36 dummy variables for combinations of year and month reduced the RR for PM, but did not eliminate PM as a significant contributor to total mortality. Control of seasonality by use of a generalized additive model to adjust for time effects gave a somewhat larger RR for PM<sub>10</sub>, with small uncertainty. Figure 12-23b shows that the estimated TSP effect has little sensitivity to the inclusion of copollutants: NO<sub>2</sub>, SO<sub>2</sub>, O<sub>3</sub>.

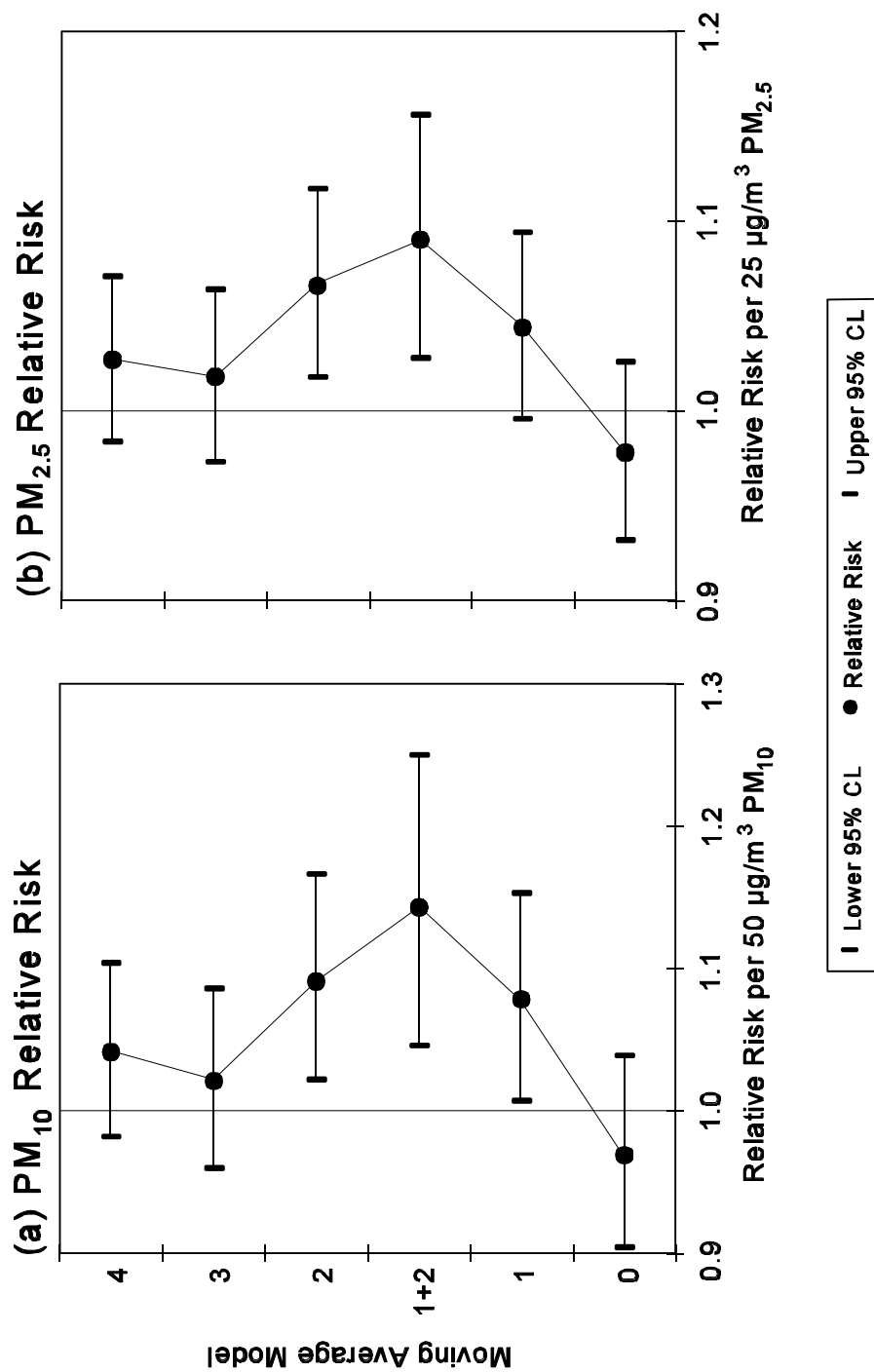
Figure 12-23c evaluates a number of lag and moving average models for PM. The relative risks corresponding to each term have been recalculated from the regression coefficients (denoted b) in their Table 8, for a basis of 100 to 150 µg/m<sup>3</sup>, by the formula

$$RR = \exp( b * \log(150/100) ),$$

with confidence limits estimated analogously. All of the PM effects are statistically significant, with the exception of the 3-day lag term in the 4-day polynomial distributed lag (PDL) model. The 0-day and 2-day single lag models and the 3-day and 4-day moving average models perform almost as well at predicting total mortality as does the PDL model, of which they are each a special case.

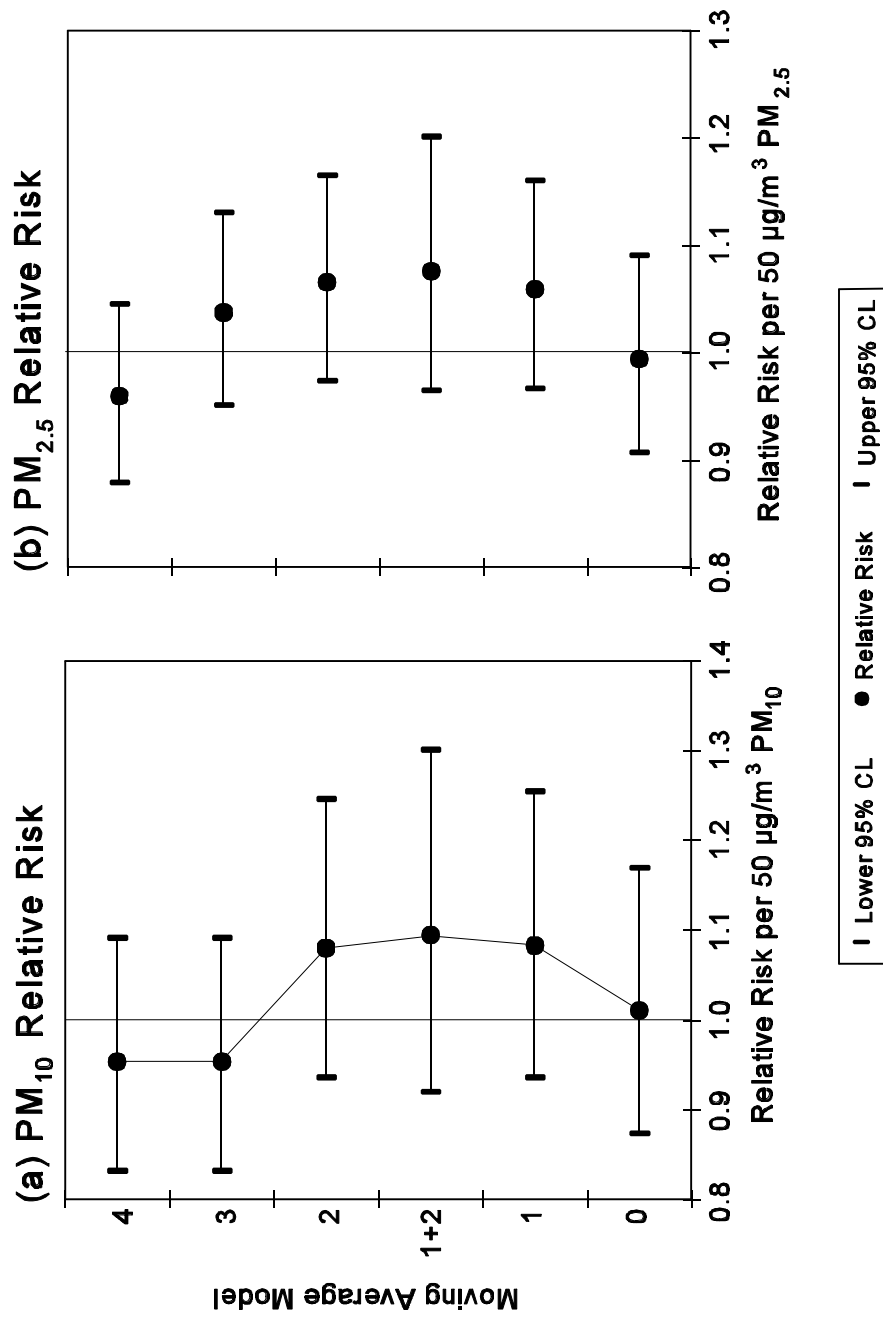
***Model Specification for the St. Louis and Eastern Tennessee Mortality Studies (Dockery et al., 1992)***

The daily mortality data for St. Louis and for eastern Tennessee analyzed by Dockery et al. (1992) were discussed in Section 12.3.1. Additional results contributing to the analysis were presented by Dockery in a report presented at the EPA-sponsored workshop on PM-related mortality in November, 1994 (Dockery, 1995). Figure 12-24a,b illustrates the sensitivity of the PM<sub>10</sub> RR to the lag time or moving average model in the Poisson regression for St. Louis total mortality, and Figure 12-25a,b shows the analogous plot for the eastern Tennessee area. Models were fitted for lags from 0 to 4 days, and for the lagged moving average from the two preceding days. The lag 1 and 2 RR estimates for St. Louis, and the lagged 2-day moving average were statistically significant for the St. Louis mortality series, but no PM indicator had a statistically significant RR for PM<sub>10</sub> in the eastern Tennessee mortality series even though the RR estimates were numerically very similar.



**Figure 12-24. Relative risk of total mortality for particulate matter in St. Louis, as a function of moving average and lag times: (a) PM<sub>10</sub> and (b) PM<sub>2.5</sub>.**

Source: U.S. EPA graphical depiction of results from Dockery et al. (1992) and Dockery (1995).



**Figure 12-25. Relative risk of total mortality for particulate matter in eastern Tennessee as a function of moving average and lag times: (a) PM<sub>10</sub> and (b) PM<sub>2.5</sub>.**

Source: U.S. EPA graphical depiction of results from Dockery et al. (1992) and Dockery (1995).

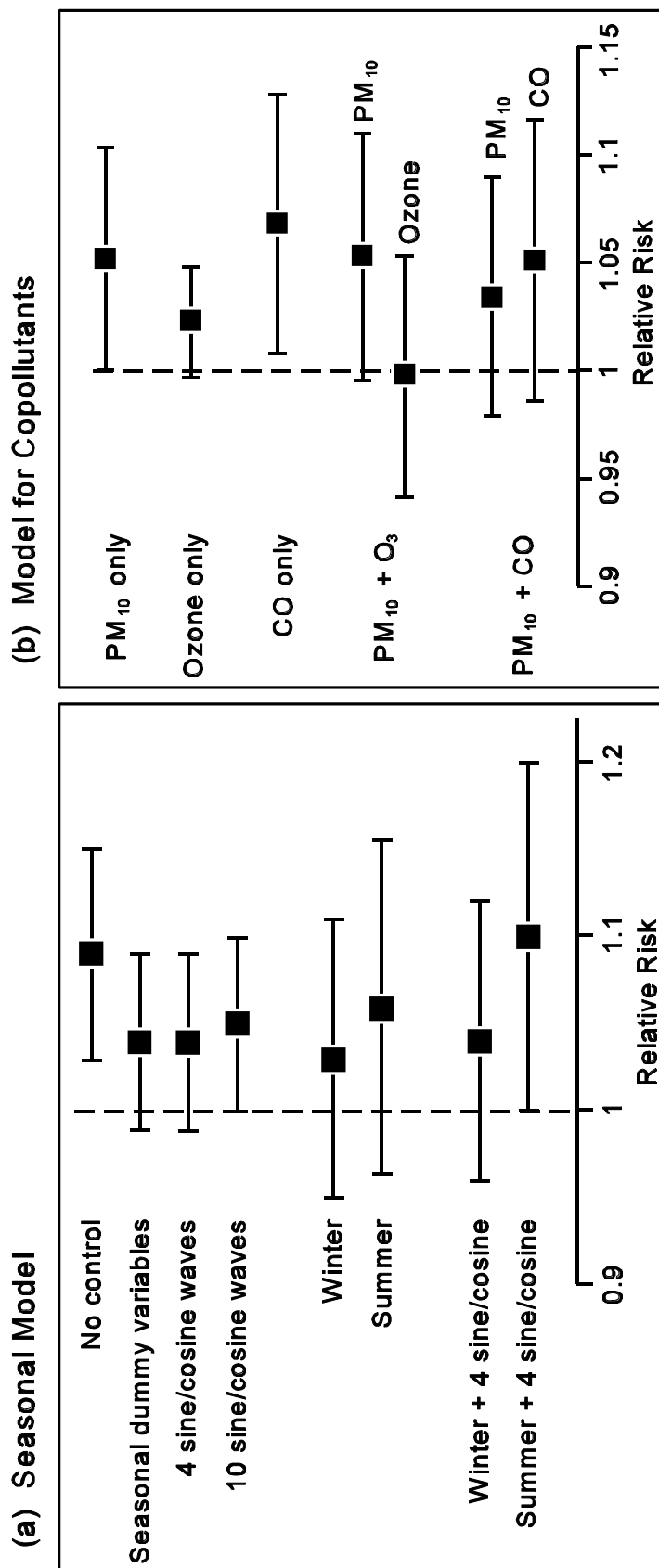
Longer-term moving averages were not evaluated, but the effects of  $PM_{10}$  would probably have been much smaller than the RR calculated using the average of 1- and 2-day lagged PM. As in the Utah Valley and Santiago studies, PM lag structure needed to be identified in order to obtain a significant PM effect.

***Model Specification for the New York City Respiratory Mortality Study  
(Thurston and Kinney, 1995)***

Thurston and Kinney (1995) compared several Gaussian OLS time series models with a Poisson regression model, using respiratory mortality data for New York City for 1972 to 1975. Time series were done using both unfiltered mortality and pollution data, and filtered mortality and pollution time series using a 19-day moving average. Analyses were done using year-round unfiltered OLS, April-September OLS, April-September filtered OLS, April-September adjustments by sines and cosines, and April-September Poisson regression adjusted with sines and cosines. During the April-September ozone season, the unfiltered OLS model showed a strong significant COH effect, but the COH effect size decreased to small and nonsignificant values when the filtered or detrended analyses were performed. The ozone effect size decreased somewhat from the unfiltered OLS analysis, but was similar in magnitude and statistically significant using filtered or detrended OLS, or Poisson regression models.

***Model Specification for the Los Angeles Mortality Studies  
(Kinney et al., 1995; Ito et al., 1995)***

Kinney et al. (1995) have discussed a number of important model specification issues for an air pollution time series model. Figure 12-26a,b, taken from their paper, shows the RR estimates for  $100 \mu g/m^3$   $PM_{10}$ , with alternative methods to control for temporal cycles. In general, most such adjustments for seasonal cycles using dummy variables or Fourier series (sines and cosines) reduced the RR slightly. Subsetting the data into winter and summer groups increased the uncertainty, but did not greatly affect the RR estimate. However, the summer-only RR adjusted with 4 sine/cosine terms was larger than the unadjusted annual RR, and statistically significant. Figure 12-26b shows the results of including co-pollutants,  $O_3$  and CO. Including  $O_3$  in the model, along with  $PM_{10}$ , did not



**Figure 12-26. Relative risk of total mortality for PM<sub>10</sub> Los Angeles, as a function of (a) seasonal model and (b) models including co-pollutants.**

Source: Adapted from Kinney et al. (1995).

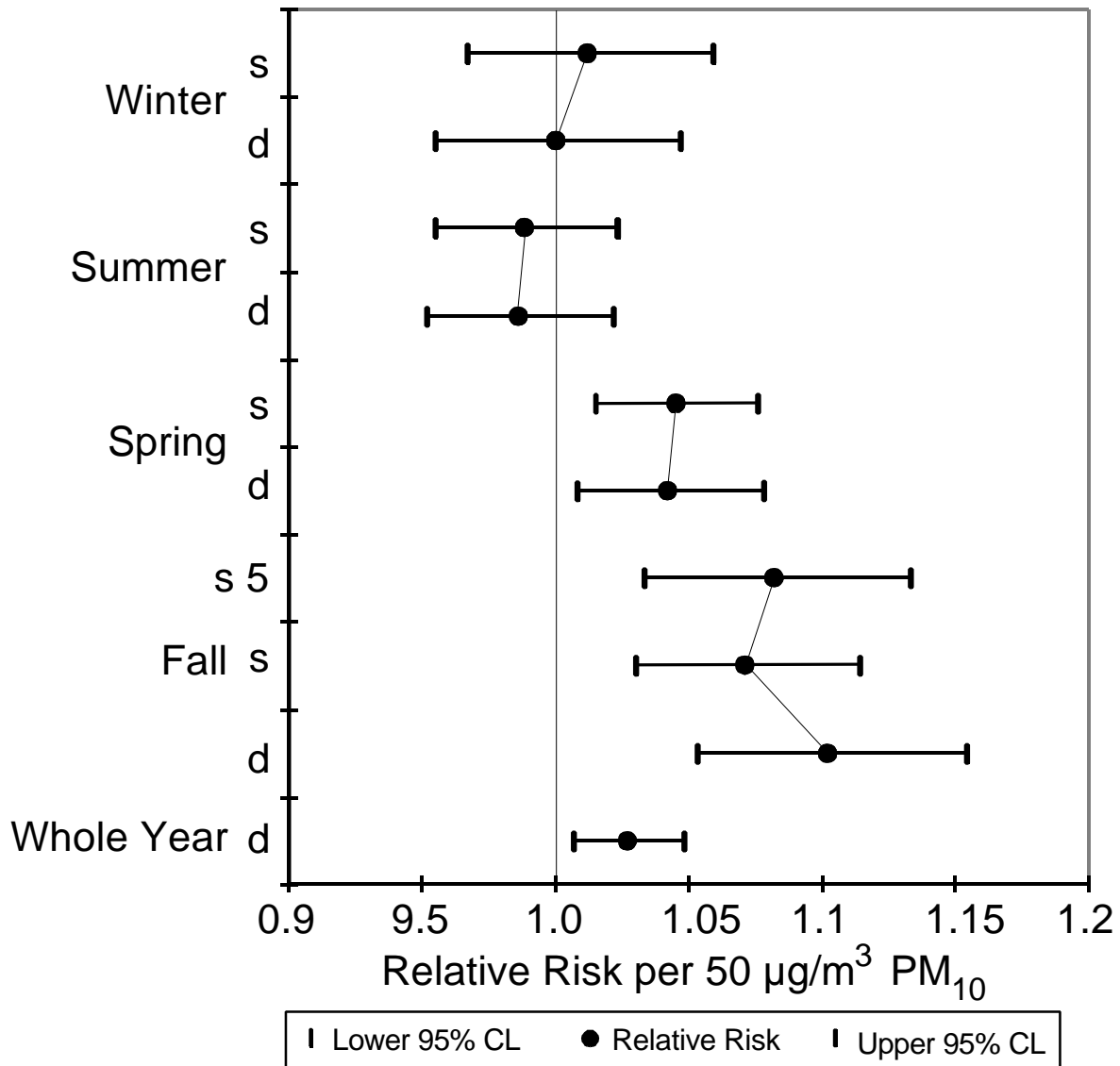
change the RR for PM, but increased its uncertainty slightly so that the RR for PM became only marginally significant (two-tailed test,  $p < 0.05$ ). Including CO in the model reduced the RR for PM, which was also less significant. CO and O<sub>3</sub> were too highly correlated to use in a three-pollutant model.

Ito et al. (1995) have evaluated alternative model specifications for combining data from a network of urban monitoring stations, when one station collects data daily and others at an irregular schedule, such as once-every-6-days with different days at different stations. While an important subject, this is not the primary source of concern about possible model misspecification. The optimal use of monitoring data distributed over space and time is more likely to appear as a problem in exposure measurement error arising when any surrogate is used instead of the actual individual exposure.

***Model Specification for the Chicago Mortality Studies  
(Ito et al., 1995; Styer et al., 1995)***

Styer et al. evaluated several alternative models for the Chicago PM<sub>10</sub> study discussed in Section 12.3.1, including models that assess the effects of dividing data by season. Figure 12-27 shows the RR for total elderly mortality per 50  $\mu\text{g}/\text{m}^3$  of PM<sub>10</sub> in ten different models. Model 0 is their basic best-fitting model using all of the data and assuming a common PM effect for all seasons. The next eight models deal with pairs of model specifications for PM in each season. Models 1, 4, 6, 8 are based on a single model using all of the data with dummy variables for each season that allows separate PM effects in fall, spring, winter, and summer respectively. Models 2, 5, 7, and 9 are similar models fitted independently using subsets of the data for each season. Model 3 is also a separate model for elderly mortality in fall, similar to Model 2 except that the moving average for PM is 5 days, whereas all of the other models used 3-day moving averages. In general, the RR for each season did not show large differences when different estimation methods were used, but there were large differences among seasons in these analyses. The only statistically significant RR were for fall and spring. The PM RR for winter and summer seasons did not differ significantly from 1.0.

Ito et al. (1995) also evaluated alternative model specifications for combining data from a network of urban monitoring stations in Chicago. Relative risks for models with daily



**Figure 12-27. Relative risk of total mortality for  $PM_{10}$  in Chicago as a function of the model for seasons. Abbreviations: d, all of the data; s, subset of the data; S5, for models of 3 to 5 day moving average, whereas all other models used 3-day moving average.**

Source: U.S. EPA graphical depiction of results from Styer et al., 1995.

$PM_{10}$  were statistically significant using any of several alternative averaging models, such as averaging from all non-missing sites or averaging from all sites using regression-imputed  $PM_{10}$  for missing sites. Data from some individual sites also gave significant PM effects, but models using

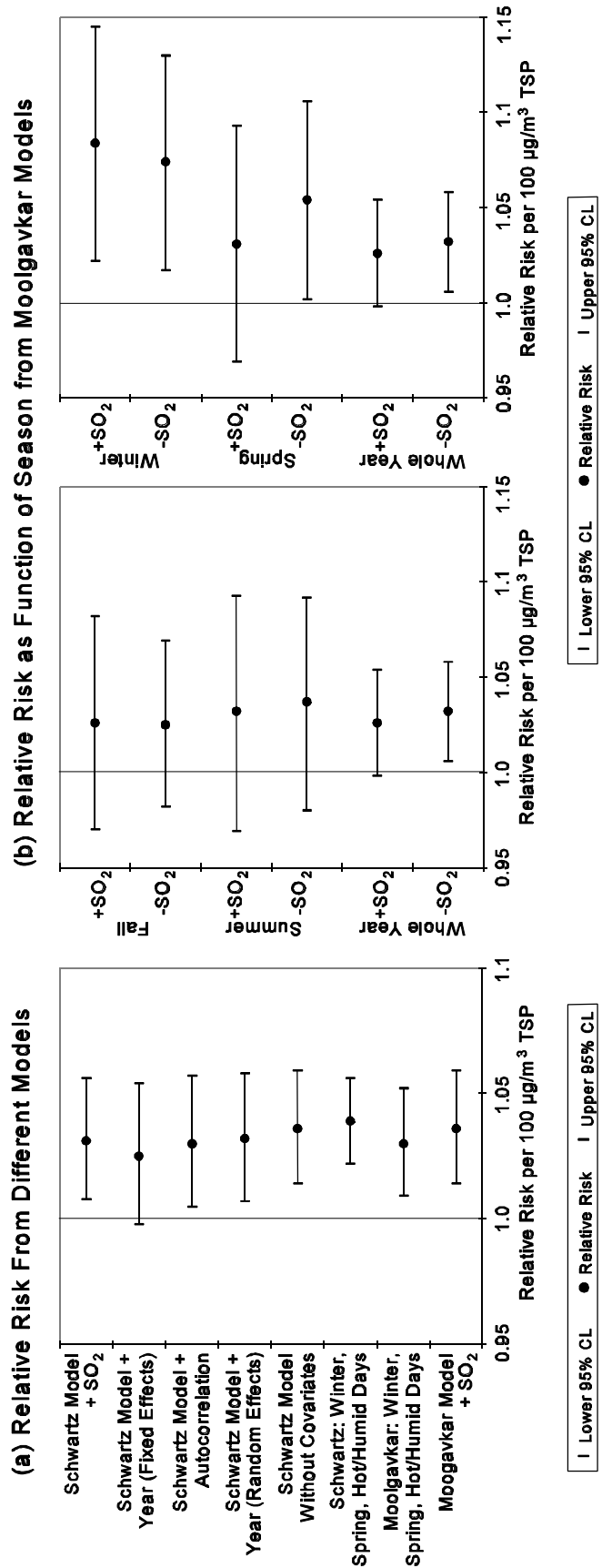
every-6-day data were generally not significant, typically because the estimated RR had greater uncertainty when only 1/6 as many data were available.

***Model Specification for the Steubenville Mortality Studies (Schwartz and Dockery, 1992b; Moolgavkar et al. 1995a)***

Two papers have assessed alternative treatments of a single data base, air pollution and mortality data from Steubenville, OH for 1974-1984 and, more recently, for 1981-1988 (Moolgavkar et al. 1995a). The initial analyses by Schwartz and Dockery (1992b) evaluated several Poisson regression model specifications, including a basic model with mean temperature and dewpoint (same day and lagged one day), and seasonal indicators. Neither same-day nor lagged temperature and dewpoint were statistically significant, nor the square of these variables, nor indicators for hot days ( $> 70^{\circ}\text{F}$ ). However, humidity measured by mean dewpoint temperature was nearly statistically significant at the  $p \leq 0.05$  level, and an indicator for days that were both hot ( $> 70^{\circ}$ ) and humid (dewpoint  $> 65^{\circ}$ ) was a statistically significant predictor of mortality. Sensitivity analyses included putting both average of same-day and previous day TSP and  $\text{SO}_2$  in the model, omitting weather and season variables, including year of the study as either a random effect or as a fixed effect (no year was significant) and including an autocorrelation structure. As expected, including  $\text{SO}_2$  reduced the TSP effect, but the decrease was small; RR for TSP decreased from 1.04 without including  $\text{SO}_2$  to 1.03 per  $100 \text{ ug}/\text{m}^3$  when  $\text{SO}_2$  was included, and the  $\text{SO}_2$  coefficient was not significant whereas the TSP coefficient was still statistically significant. As shown in Figure 12-28a, these had little effect on the estimated relative risk for  $100 \text{ ug}/\text{m}^3$  TSP. This paper also demonstrated the use of TSP quartiles for displaying a relationship between the PM indicator and adjusted mortality or morbidity. However, TSP was used as a continuous covariate in the models because the grouping of continuous measurements into groups or categories must involve a loss of information, whether large or small.

Moolgavkar et al. (1995a) evaluated a number of Poisson regression models, with particular emphasis on seasonal subsets of the data. The whole-year models analogous to those of Schwartz and Dockery (1992b) are also shown in Figure 12-28a. The results are close to those of Schwartz and Dockery, but are not identical. The RR for  $100 \text{ ug}/\text{m}^3$  TSP are somewhat smaller, but the decrease is only from about 1.032 to 1.025 when  $\text{SO}_2$  is included in the model. These

coefficients are for what Moolgavkar et al. define as the "restricted" mortality data set, which consists of deaths in Steubenville of people who resided



**Figure 12-28. Relative risk of total mortality for total suspended particle (TSP) in Steubenville: (a) different models (left) and (b) as a function of season (center, right).**

Sources: U.S. EPA graphical depiction of results from Schwartz and Dockery (1992b) and Moolgavkar et al. (1995a).

there. This is comparable to the data set used by Schwartz and Dockery in this study, and by Schwartz or Dockery and their associates in many other studies. The argument for use of the "restricted" mortality data is that community-based air monitors provide better exposure indicators for people who live in the community most of the time, as opposed to commuters or to other visitors who die in the community. Also, since many metropolitan areas contain medical facilities that may be better equipped than those in more remote areas, it is possible that some excess number of the deaths in elderly or ill patients transported from the more remote areas occur in urban centers such as Steubenville. Moolgavkar et al. (1995a) also show results for analyses of "full" mortality data, which includes individuals who did not reside in the location at which they died.

It is clear that season-to-season effects are present in these data. Schwartz and Dockery found that winter and spring mortality was significantly higher than summer and fall mortality. Moolgavkar separated the analyses by season. He found that whole-year RR for TSP was nearly the same as RR in the separate summer and fall models, with or without SO<sub>2</sub> in the model, and nearly the same in the spring model when SO<sub>2</sub> was included. However, TSP coefficients were higher in the winter, and in the spring model when SO<sub>2</sub> was not included. In fact, as shown in Figure 12-28b, the RR for TSP increased slightly in the winter model when SO<sub>2</sub> was included.

There is a possibility that the weather models used by Schwartz and Dockery, and by Moolgavkar et al. are not adequate to remove all of the seasonal effects. It is possible that additional variance reduction could have been achieved with the use of additional weather data, emphasizing more extreme conditions than the very moderate cutpoints of temperature and dewpoint, since temperature extremes are known to have effects on mortality (Kalkstein, 1991; Kalkstein et al., 1995; Kunst et al., 1993). Variables used by other investigators, such as barometric pressure, could have been tested. The flexibility of the model to fit nonlinear relationships could be improved by the use of nonparametric or semi-parametric models, and classifying data by synoptic weather category may provide a useful alternative approach to evaluating the interaction between season and weather.

Moolgavkar found that the TSP coefficients were not statistically significant (two-tailed tests at 0.05 level) in any season except winter, nor in the whole-year model, when SO<sub>2</sub> was included in the model. However, the season-by-season TSP coefficients were not tested in a whole-year model. Part of the non-significance may be attributable to the fact that confidence

intervals for a regression parameter in a separate seasonal model, with about 1/4 of the data in a whole-year model, may be on the order of twice (= reciprocal square root of 1/4) as wide as the confidence interval for the corresponding season-by-pollutant regression coefficient in a whole-year model, everything else being equal.

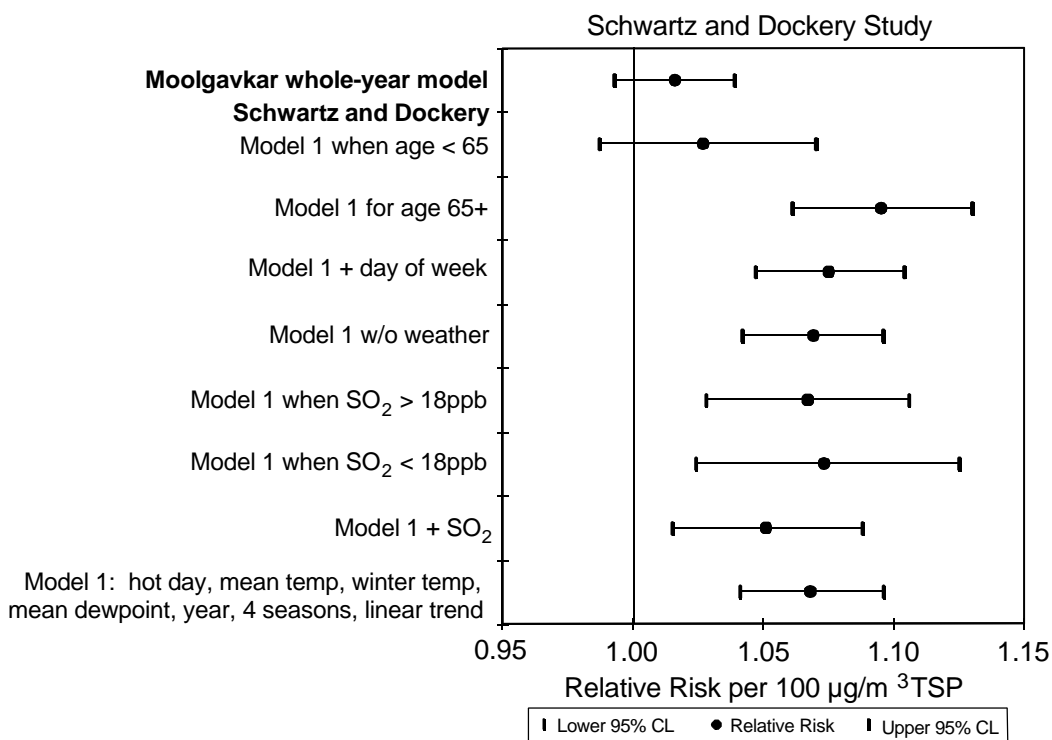
The method of adjusting the mortality series for weather effects and for other time-related effects (detrending) may be important in explaining why the RR estimates for TSP vary seasonally and why those derived by Moolgavkar et al. are quantitatively different from those derived by Schwartz and Dockery (1992b), even though the differences are small in these studies. There may exist some residual confounding with weather, since other studies have found that substantial adjustment of weather by use of temperature and dewpoint categories, or nonparametric smoothers of temperature, humidity, and time can effectively eliminate seasonal variations in residuals and in PM effect. Even so, the estimated TSP effect on RR of mortality is positive in most seasons, even in Steubenville models including the collinear co-pollutant SO<sub>2</sub>. No adjustments were made for other pollutants such as CO, NO<sub>x</sub>, and O<sub>3</sub>.

These analyses of the Steubenville data set are primarily useful for demonstrating the results of different data analysis strategies and methods, since the PM indicator was TSP, not PM<sub>10</sub>. These analyses have shown the desirability of adequately adjusting the analysis of pollution effects for weather and for long-term and medium-term time trends and variations. When co-pollutants were evaluated, it was evident that only part of the TSP effect could be attributed to SO<sub>2</sub>. Differences in RR of TSP between analyses presented in the two papers are not regarded as large.

***Model Specification for Philadelphia Mortality Studies (Schwartz and Dockery, 1992a; Li and Roth, 1995; Moolgavkar et al. 1995b; Wyzga and Lipfert, 1995b; Cifuentes and Lave, 1996)***

Several papers have recently appeared that allow assessment of alternative treatments of a single data base, the air pollution and mortality data from Philadelphia for the years 1973 to 1980, and more recently 1981 to 1988 (Moolgavkar et al. 1995b). The initial analyses by Schwartz and Dockery (1992a) evaluated several Poisson regression model specifications, including a basic model with mean temperature and dewpoint (lagged one day), winter season temperature (same day), and an indicator for hot days (> 80 F). Sensitivity analyses included putting both average of same-day and previous day TSP and SO<sub>2</sub> in the model, stratifying analyses as above or below median SO<sub>2</sub> level (18 ppb), omitting weather and season variables, and including day of week. As

shown in Figure 12-29, these had little effect on the estimated relative risk for  $100 \mu\text{g}/\text{m}^3$  TSP. RR for mortality in the elderly was greater than for other age groups. A more detailed assessment of the age structure was presented by Schwartz (1994c), showing clearly that there was increased mortality in ages 65 to 74, and again higher at ages 75+. There was also significantly increased mortality at ages 5 to 14 years, based on a small number of cases. This paper also demonstrated the use of TSP quantiles for displaying a relationship between the PM indicator and adjusted mortality or morbidity. However, TSP was used as a continuous covariate in the models because the grouping of continuous measurements into groups or categories must involve a loss of information, whether large or small.

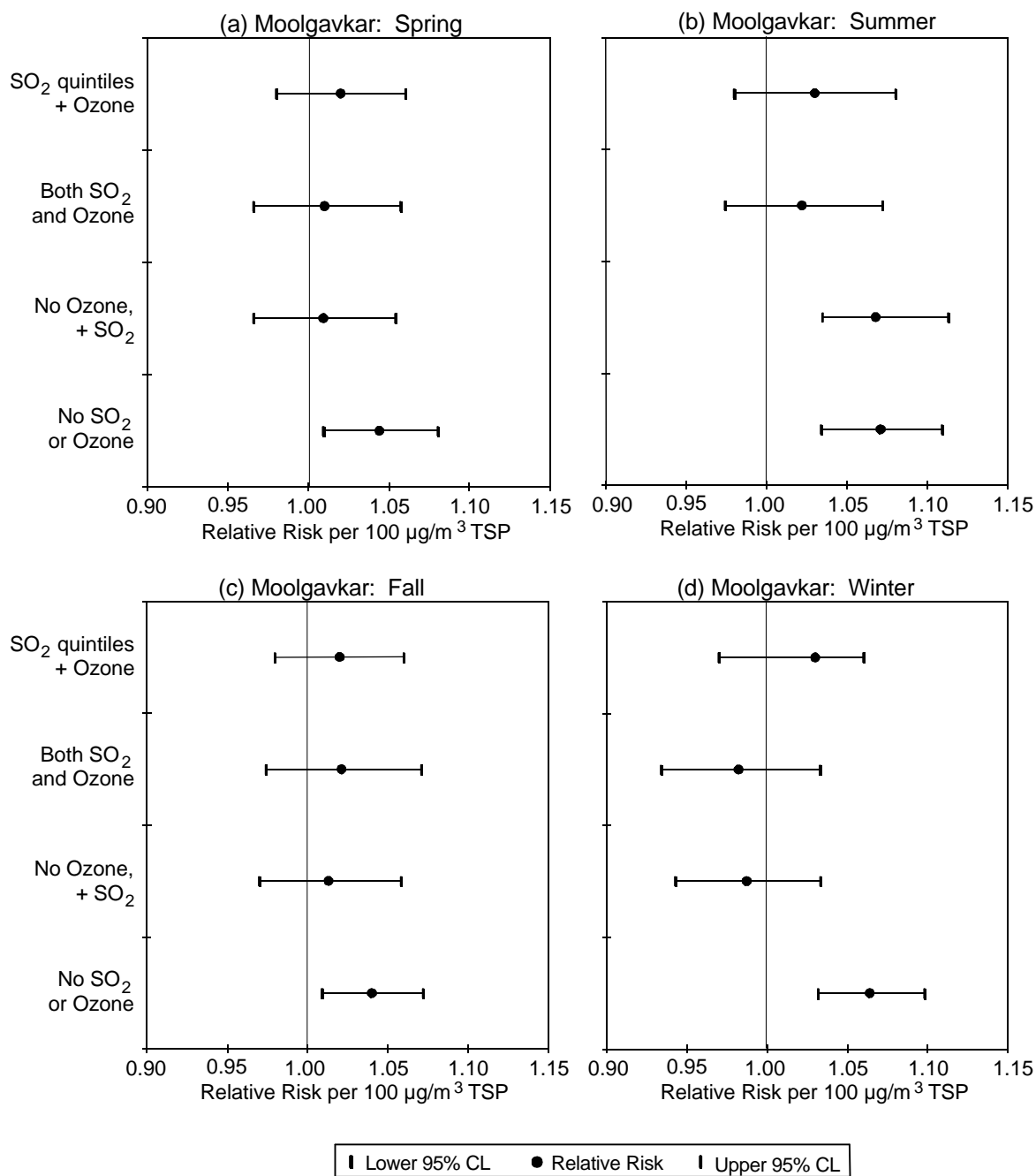


**Figure 12-29. Relative risk of total mortality for total suspended particles (TSP) in Philadelphia.**

Sources: U.S. EPA graphical depiction of results from Schwartz and Dockery (1992a) and Moolgavkar et al. (1995b).

Li and Roth (1995) reanalyzed these data, but only reported results in the form of t-statistics. A wide range of model specifications were tested, although some models (such as those using deviations from mean values for day of year, or from monthly average) appear to assume an unrealistic level of seasonal recurrence of air pollution and weather effects in the model most directly comparable to the Poisson regression models used by Schwartz and Dockery (1992a). The autoregressive model they denoted AR(6) was somewhat comparable to models tested in the London analyses of Schwartz and Marcus (1990). However, the models with residual deviations of mortality from 7-, 15-, or 29-day moving averages did not have comparably filtered predictors on the "right" side of the prediction equation; so the regression coefficients are not readily interpretable as predictions of mortality deviations from mean pollution levels. The Poisson log models that are most comparable to those used by other investigators involved comparisons of model specifications for averaging times. The results only indicate statistical significance by use of statistics, not effect size in any form more useful in epidemiologic studies (Greenland et al., 1986). In a model that includes TSP, SO<sub>2</sub>, and O<sub>3</sub>, statistical significance of TSP is clearly highest with the moving average of 0+1 day lags, and diminishes sharply for all pollutants when longer lags are included. Models with longer weather averages are also more predictive. The lower significance of the TSP term may be related to the fact that it may have greater exposure measurement error than the gaseous pollutants. The models evaluated in this paper were not adjusted for collinearity, even though there are some fairly strong collinearities in the data, such as between TSP and SO<sub>2</sub> and between temperature and ozone, so that inclusion of several collinear variables is almost certain to greatly inflate the variance and thus reduce the statistical significance of many of the regression coefficients.

Moolgavkar et al. (1995b) evaluated a number of Poisson regression models, with particular emphasis on seasonal subsets of the data. These are shown in Figure 12-30a-d. It is clear that season-to-season effects are present in these models. The models were adjusted for weather and time trend by using quintiles of temperature and indicators of year. There is a possibility that the weather model is not adequate to remove all of the seasonal effects. Subdividing the temperature range by quintiles will result in three or four closely spaced quintiles corresponding to moderate temperatures which have little effect on mortality, and will not adequately take into account temperature extremes. Quintiles of temperature are not



**Figure 12-30. Relative risk of total mortality for total suspended particles (TSP) in Philadelphia, in the (a) spring, (b) summer, (c) fall, and (d) winter.**

Source: U.S. EPA graphical depiction of results from Moolgavkar et al., 1995b.

given here, but Li and Roth (1995) report values of maximum temperature at the 10th, 25th, 50th, 75th, and 90th percentiles as 37, 48, 63, 78, and 84 degrees F; and Schwartz and Dockery (1992a) report mean temperature percentiles corresponding to 25, 36, 52, 66, and 73 degrees F, respectively. This paper finds a significant effect for the highest quintile in the summer and the lowest quintile in the other seasons, suggesting that additional variance reduction could have been gained by the use of additional weather data, emphasizing more extreme conditions than the 20th and 80th percentiles and possibly including information on dewpoint or barometric pressure (as used by other investigators). In general, replacing numeric data by grouped equivalents such as quintile classes involves some loss of information. The loss of information may be acceptable if there is a corresponding increase in the flexibility of the model to fit nonlinear relationships, but in this instance the loss of information may be substantial since extreme temperatures are known to have a quantifiable and increasing relationship with mortality as the temperatures become more extreme (Kunst et al., 1993). The method of adjusting the mortality series for weather effects and for other time-related effects (detrending) may be important in explaining why the RR estimates for TSP vary seasonally and are quantitatively different from those derived by Schwartz and Dockery (1992a). There may exist some residual confounding with weather, since other investigators have found that substantial adjustment for weather by use of temperature and dewpoint categories or by nonparametric smoothers of temperature, humidity, and time can effectively eliminate seasonal variations in residuals and in PM effect. Even so, the estimated TSP effect on RR of mortality is positive in most seasons, even in models including collinear co-pollutants  $\text{SO}_2$  and  $\text{O}_3$ .

Neither the Schwartz and Dockery (1992a) study nor the Moolgavkar et al. (1995b) study allows a complete assessment of the actual role of co-pollutants as confounders of a PM effect. While  $\text{SO}_2$  is not as strongly correlated with temperature as is  $\text{O}_3$ , it is also subject to weather conditions that affect atmospheric dispersion along with TSP. Therefore, if there is an incorrect assignment of weather effects on mortality, some part of the mortality that could have been explained with weather-related variables will probably be allocated to various other predictors of mortality used in the models, especially TSP and the co-pollutants. The development of a predictive model for mortality using weather and other time-varying covariates would probably have required use of humidity, since humidity along with temperature had been predictive of mortality in earlier studies, such as for London (Schwartz and Marcus, 1990) and Steubenville

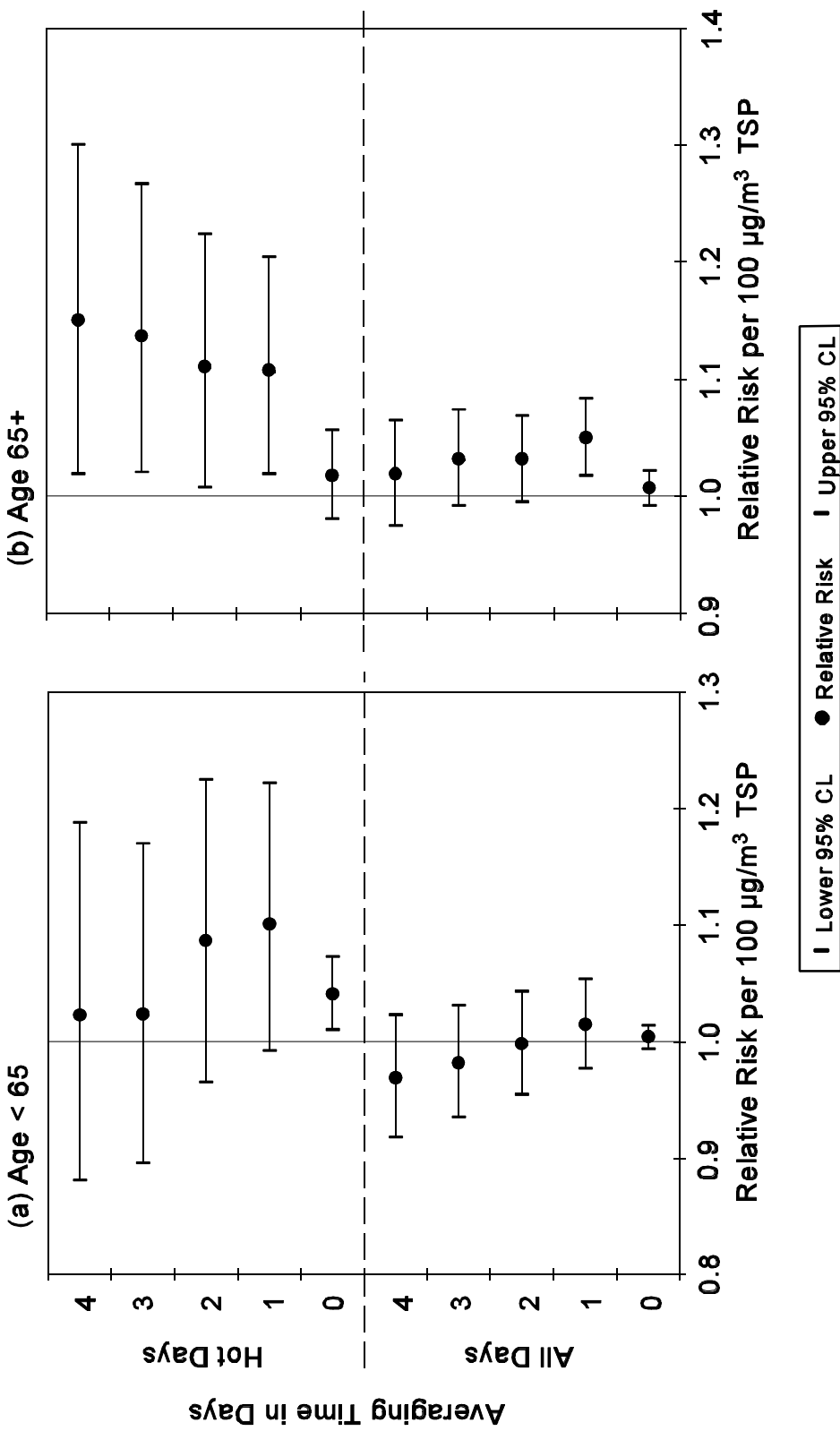
(Schwartz and Dockery, 1992b). If confounding can be explained by an unobserved (or in this case, unused) covariate, then omission of humidity from any of the models in the Moolgavkar et al. (1995b) study is certainly another candidate explanation for the differences in results between these papers. However, both papers may also have provided an inadequate adjustment for other medium-term effects on a scale longer than a day and shorter than a season or quarter, such as for epidemics. The use of nonparametric smoothers such as LOESS, or GAM models of time, would allow subtraction of such trends. Even a simple alternative, such as including a dummy variable for every month in every year (96 parameters for the 1973-1980 series; another 96 parameters for the 1981-1988 series) would probably have greatly improved the ability of these analyses to evaluate short-term responses to short-term changes in air pollution and weather. The parameters that relate mortality to pollution and weather over intervals of a few days were likely the same or similar over periods of some years and would require only a few more parameters. In view of these questions, we regard potential confounding among TSP, SO<sub>2</sub>, and summer ozone in Philadelphia that was identified in the Moolgavkar et al. (1995b) study as possible, but not yet proven.

Another unresolved issue is that TSP may have relatively larger exposure measurement error than the gaseous pollutants. Since TSP includes large particles, TSP levels are more associated with local sources and transport near the air pollution monitors and show a weaker correlation with TSP at other monitors than is the case for smaller particles. In particular, TSP would be expected to show less correlation within the Philadelphia area than would PM<sub>10</sub>, and even less yet than would PM<sub>2.5</sub> across the area. Therefore, TSP may be less predictive of individual PM exposure than the smaller size PM indicators in Philadelphia. Since variables with larger exposure measurement error are more likely to show attenuated effects (bias towards smaller RR) than covariates with smaller measurement errors, it is at least possible that SO<sub>2</sub> may spuriously appear to be a more important predictor of pollution-related mortality than does TSP. There does not seem to be any way to evaluate these possibilities from the published reports.

Wyzga and Lipfert (1995b) also reanalyzed the Philadelphia time series data for 1973 to 1990, using Gaussian OLS regression models with time-lagged predictors. In view of the moderately large number of deaths per day (21 deaths at ages less than 65 years, 34.5 deaths at ages 65 and older), the OLS regression coefficients are probably sufficiently accurate approximations to regression coefficients estimated from Poisson regression models. They

evaluated model specifications for daily mortality, log mortality, and deviations of mortality from 15-day moving averages. The regression models were adjusted for maximum temperature dummy variables in 6 categories, winter season, daily changes in barometric pressure, and time trend. Maximum hourly  $O_3$  was evaluated as a co-pollutant. The RR estimates for TSP were calculated using regression coefficients and standard errors in their Table 3, plus data from their Figures 14 and 20. Figure 12-31a shows RR for ages <65 years, Figure 12-31b for ages 65+ years, for all days ( $N = 2380$ ) and for  $N=390$  hot days (maximum temperature at least 85 degrees), for different averaging times. The largest and most significant estimates of TSP effect, measured as deviations from 15-day moving averages, are in the elderly, especially on hot days. For the elderly on hot days, the TSP effect is nearly the same for averaging times from 2 to 5 days on hot days, but the 0+1 day moving average has only slightly greater statistical significance than the 0+1+2+3 and 0+1+2+3+4 day averages. When all days are considered, the RR for TSP is only half as large and statistically significant only for 0+1 day TSP averages. For deaths at age <65, none of the all-day TSP RR values were significant; on hot days, the 0+1 average TSP was nearly significant, and the 0+1+2 day average TSP effect nearly as large, but other RR estimates were much smaller. The estimates were not calculated using filtered pollution series, but the moving averages of TSP had some of the same effect of removing long-term trends and effects. These estimates are in general similar to those found by Schwartz and Dockery, but larger differences were found for other model specifications. This paper did not attempt to include  $SO_2$  as a covariate, since TSP was clearly collinear with  $SO_2$ .

These analyses of the Philadelphia data set are primarily useful for demonstrating the results of different data analysis strategies and methods, since the PM indicator was TSP, not  $PM_{10}$ . These analyses have shown the desirability of adequately adjusting the analysis of pollution effects for weather and for long-term and medium-term time trends and variations. When co-pollutants were evaluated, it was evident that only part of the TSP effect could be attributed to  $O_3$ , and that the  $O_3$  effect was more nearly confounded with temperature and season than with TSP. However, there was a substantial degree of confounding between



**Figure 12-31. Relative risk of mortality for TSP in Philadelphia, as a function of age, averaging time, and temperature: (a) age < 65; (b) age > 65.**

Source: U.S. EPA graphical depiction of results from Wyzga and Lipfert (1995b).

TSP and SO<sub>2</sub> effects, which could be separated in some analyses but not in all analyses. The best averaging time for pollution was 0+1 days, but longer averages seemed useful in estimating RR among the elderly during hot weather.

### ***Models with Additive Linear Specification for Multiple Pollutants***

The relationship between Philadelphia mortality and some potentially confounding pollutants has recently been reexamined by Samet et al. (1996a). The results from tables 7,8, and 11 of their report are summarized in Table 12-26. They fitted models for total mortality, cardiovascular mortality, respiratory mortality, and mortality for other non-external causes, for the period 1974 to 1988. Models were fitted for whole-year data using adjustments for weather, season, time trends, and for five pollutants: TSP, SO<sub>2</sub>, O<sub>3</sub>, NO<sub>2</sub>, and CO. The results shown here in Table 12-26 are for whole-year total mortality averages of current-day and previous-day pollutant concentrations, and a lagged CO variable denoted LCO that includes the 2-day average CO from 3 and 4 days earlier, as predictors of total mortality in a Poisson regression model with seasonal adjustments. They report results from their models somewhat differently than in this document, as the percent increase in mortality per increase over the inter-quartile range (IQR) of the pollutant. While we have established standard increments for TSP and SO<sub>2</sub>, we have not defined standard increments for the effects of the other pollutants and so we report their results in the same form as in their report. The most important findings from Samet et al. (1996a) are: (a) CO never has a significant concurrent effect; (b) LCO has a stable significant effect; (c) O<sub>3</sub> has a stable significant effect; (d) the TSP coefficient is reduced if SO<sub>2</sub> is in the model increased when NO<sub>2</sub> is in the model; (e) the SO<sub>2</sub> coefficient is reduced when TSP is in the model and increased when NO<sub>2</sub> is in the model; and (f) the NO<sub>2</sub> coefficient is small and not significant unless TSP or SO<sub>2</sub> are in the model.

Table 12-26 shows the IQR effects for 17 models reported by Samet et al. (1996a). Model 1 shows the regression coefficients using all six pollutant averages. The superscript "1" shows that the coefficients would be regarded as statistically significant, with the t statistic (ratio of coefficient estimate to asymptotic standard error estimate) between 2 and 4, except for TSP with t = 1.962, and CO which is not at all statistically significant. Models 2 and 3 show results with omission of LCO and omission of CO respectively. To compare

**TABLE 12-26. EXCESS RISK ESTIMATES FOR SIX AIR POLLUTION INDICES, FOR PHILADELPHIA, 1973-1988. COEFFICIENTS ARE PERCENT EXCESS TOTAL MORTALITY PER INTERQUARTILE RANGE IN POLLUTANT CONCENTRATION.**

Model	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
P	TSP	TSP	TSP	TSP	TSP	TSP	TSP	TSP	TSP	TSP	---	---	---	---	---	---	---
O	SO <sub>2</sub>	SO <sub>2</sub>	SO <sub>2</sub>	SO <sub>2</sub>	---	SO	---	---	---	---	SO	SO <sub>2</sub>	SO <sub>2</sub>	SO <sub>2</sub>	---	---	---
L	O <sub>3</sub>	O <sub>3</sub>	O <sub>3</sub>	---	---	---	O	---	---	---	O	---	---	---	O	O <sub>3</sub>	O <sub>3</sub>
U	NO <sub>2</sub>	NO <sub>2</sub>	NO <sub>2</sub>	---	---	---	---	NO	---	---	---	NO	---	---	---	NO	---
T	CO	CO	---	---	---	---	---	---	CO	---	---	---	CO	---	---	---	CO
A	LCO	---	LCO	---	---	---	---	---	---	LCO	---	---	---	LCO	LCO	---	---
N	TSP	1.04	0.95	1.06	0.74	1.15	1.15	1.79 <sup>2</sup>	1.43 <sup>1</sup>	1.21 <sup>1</sup>	---	---	---	---	---	---	---
T	SO <sub>2</sub>	1.08 <sup>1</sup>	1.08 <sup>1</sup>	1.08 <sup>1</sup>	0.60	---	1.08	---	---	---	1.05	1.45 <sup>1</sup>	1.23 <sup>1</sup>	1.12 <sup>1</sup>	---	---	---
S	O <sub>3</sub>	1.95 <sup>1</sup>	2.15	1.91	1.15 <sup>1</sup>	---	---	2.04	---	---	2.25	---	---	---	2.11	2.27 <sup>1</sup>	2.37 <sup>1</sup>
	NO <sub>2</sub>	-1.14 <sup>1</sup>	-1.15 <sup>1</sup>	-1.10 <sup>1</sup>	---	---	---	-0.93	---	---	---	-0.63	---	---	---	0.14	---
	CO	0.08	0.09	---	---	---	---	---	-0.54	---	---	---	-0.38	---	---	---	0.27
	LCO	1.07	1.10	1.10	1.10	---	---	---	---	1.17	---	---	---	1.16	1.04 <sup>1</sup>	---	---
AIC <sup>3</sup>	---	74.9	66.5	---	81.7	82.0	74.4	---	---	---	72.5	---	---	---	71.4	78.8	78.7

<sup>1</sup>2 ≤ |t| < 4, except for Model 1, which has t = 1.04/0.53 = 1.962 from Table 11.

<sup>2</sup>|t| ≥ 4

<sup>3</sup>AIC - 16,400, from Table 8, where the Akaike Information Criteria (AIC) assesses goodness of fit.

Source: Samet et al. (1996a).

competing mortality prediction models, Samet et al. (1996a) used Akaike's Information Criterion (AIC) (15, 16). This index of model fit combines the deviance, which measures the fidelity of the model predictions to the observed data, with a penalty for adding more predictor variables. In the comparison of two models A and B, the model with lower AIC is preferred. If the AIC for model A is 5(10) units smaller than that for model b, this means that a new observed mortality series would be 10(150) times more likely to have occurred under model a than model b. Model 4 shows that fitting total mortality only with TSP and SO<sub>2</sub> results in greatly reduced and non-significant coefficients, although the TSP coefficient is reduced less than is the SO<sub>2</sub> coefficient. Model 5 shows that fitting the mortality time series with only TSP produces a goodness of fit that is somewhat inferior to the goodness of fit of Models 2 and 3 with 5 pollutants, where the AIC for Model 5 is 16,481.7 compared to AIC = 16,474.9 for Model 2 and AIC = 16,466.5 for Model 3. Relatively small differences in AIC should not be overinterpreted. Model 6 with only SO<sub>2</sub> produces a slightly worse fit than Model 5. Model 7, with TSP and O<sub>3</sub>, produces a slightly better fit than Model 2 after adjusting for the fact that Model 2 includes three additional pollutants: SO<sub>2</sub>, NO<sub>2</sub>, and CO. However, Model 11 with SO<sub>2</sub> and O<sub>3</sub> produces a somewhat better fit than Model 7 with TSP and O<sub>3</sub>, and Model 15 with O<sub>3</sub> and LCO a better fit than Model 11. The other models in Table 12-26 show all pairwise combinations of pollutants including either TSP, SO<sub>2</sub>, or O<sub>3</sub>.

Samet et al. (1996a) conclude that "... a single pollutant of the group TSP, SO<sub>2</sub>, NO<sub>2</sub>, and CO cannot be readily identified as the best predictor of mortality, because concentrations of the four pollutants were moderately correlated in Philadelphia during the years of this study ... We advise caution in interpreting model coefficients for individual pollutants in models including such correlated pollutants. Insights into the effects of individual criteria pollutants can be best gained by assessing effects across locations having different pollutant mixtures and not from the results of regression models of data from single locations."

Some of the issues related to confounding from co-pollutants are discussed in Sections 12.6.3.4 and 12.6.3.5, and the usefulness of assessments from multiple sites with different pollutant mixtures is noted there. However, further study of the analyses in Samet et al. (1996a) suggests that at least some of these issues may be capable of resolution by more complete analyses of the Philadelphia data. Our purpose in evaluating the potential for confounding among co-pollutants is to determine whether different pollutants are so closely related in every season as to preclude any possibility of separating their effects on health. While confounding is not the

same as collinearity in general, there is little reason to believe that pollutant concentrations adjusted for weather and season have non-monotonic or strongly nonlinear relationships, so that we may use collinearity diagnostics as convenient characterizations for potential confounding in this case. Season-specific differences among potentially confounded pollutants may also be present. The pollutant indices used in the Poisson regression models are averages of same-day and previous-day concentrations, whereas the correlation matrices in Samet et al. (1996a) are for each single day.

EPA has evaluated the potential for copollutant confounding using the correlation matrices reported in Table 6 of Samet et al. (1996a). The authors reported partial correlation coefficients of TSP, SO<sub>2</sub>, O<sub>3</sub>, NO<sub>2</sub>, and CO adjusted for weather and time trends, for the whole year and by season. EPA carried out principal components analyses of these correlation matrices (shown in Table 12-27). The principal values of a correlation matrix are all non-negative and add up to the number of variables in the matrix, so that the average principal value = 1. Many textbooks and papers (Belsley et al., 1980) suggest that for ordinary least squares regression analyses, collinearity is unlikely to be a problem if the condition number of the correlation matrix (ratio of largest to smallest principal value) is less than about 30, or roughly speaking, if the smallest principal value is greater than about 0.05. The smallest principal value for any copollutant correlation matrix is 0.228 and the largest condition number for any season is 14.5 for winter, as shown in Table 12-28. In other words, at worst, copollutants can only moderately confound the TSP effect.

Detailed assessment of principal components of the seasonal correlation matrices in Table 12-29 shows some important similarities. First of all, O<sub>3</sub> is virtually absent from the main factor (explaining 52 to 58% of the variance of the five pollutants) for spring and autumn, and O<sub>3</sub> is the virtually unique second factor explaining 22 to 24% of the variance. Thus, O<sub>3</sub> does not confound any of the TSP or other copollutant findings for these seasons. During summer and winter, O<sub>3</sub> is a somewhat larger component of the overall pollutant factor (which only accounts for 50% of the variance), but CO is a somewhat smaller component, whereas the second principal component for summer is primarily the difference between O<sub>3</sub> and CO. The third principal component is primarily the difference between SO<sub>2</sub>

**TABLE 12-27. CORRELATION MATRICES FOR FIVE POLLUTANTS IN  
PHILADELPHIA FOR THE YEARS 1974-1988, ADJUSTED FOR  
TIME TRENDS AND WEATHER, FOR EACH SEASON**

	TSP	SO <sub>2</sub>	O <sub>3</sub>	NO <sub>2</sub>	CO
<b>Spring</b>					
TSP	1.000	0.584	0.198	0.624	0.388
SO <sub>2</sub>	0.584	1.000	0.031	0.578	0.344
O <sub>3</sub>	0.198	0.031	1.000	-0.065	-0.294
NO <sub>2</sub>	0.624	0.578	-0.065	1.000	0.664
CO	0.388	0.344	-0.294	0.664	1.000
<b>Summer</b>					
TSP	1.000	0.552	0.368	0.572	0.308
SO <sub>2</sub>	0.552	1.000	0.293	0.551	0.214
O <sub>3</sub>	0.368	0.293	1.000	0.279	0.026
NO <sub>2</sub>	0.572	0.551	0.279	1.000	0.482
CO	0.308	0.214	0.026	0.482	1.000
<b>Fall</b>					
TSP	1.000	0.697	0.134	0.757	0.564
SO <sub>2</sub>	0.697	1.000	0.035	0.660	0.442
O <sub>3</sub>	0.134	0.035	1.000	0.041	-0.241
NO <sub>2</sub>	0.757	0.660	0.041	1.000	0.657
CO	0.564	0.442	-0.241	0.657	1.000
<b>Winter</b>					
TSP	1.000	0.716	-0.367	0.700	0.574
SO <sub>2</sub>	0.716	1.000	-0.470	0.683	0.535
O <sub>3</sub>	-0.367	-0.470	1.000	-0.516	-0.462
NO <sub>2</sub>	0.700	0.683	-0.516	1.000	0.727
CO	0.574	0.535	-0.462	0.727	1.000

Source: Samet et al., 1996a.

**TABLE 12-28. PRINCIPAL VALUES OF THE PRINCIPAL COMPONENTS OF TSP  
AND ITS COPOLLUTANTS IN PHILADELPHIA FOR THE YEARS 1974-1988,  
BASED ON CORRELATION MATRICES IN TABLE 12-27**

Season	Component Number					Condition Number
	1	2	3	4	5	
Spring	2.606	1.233	0.558	0.353	0.250	10.42
Summer	2.537	1.016	0.660	0.427	0.359	7.07
Fall	2.899	1.129	0.491	0.253	0.228	12.71
Winter	3.326	0.679	0.501	0.265	0.229	14.52

Source: U.S. EPA calculations based on results reported by Samet et al. (1996a).

and CO except in summer, where it is the difference between SO<sub>2</sub> and O<sub>3</sub> plus CO. The fourth principal component is primarily the difference between TSP and SO<sub>2</sub> and accounts for 5 to 8% of the variance, which may explain in part why separating these pollutants in the absence of other information may be difficult. The fifth principal component, accounting for 5 to 7% of the pollutant variance, includes NO<sub>2</sub> as the major component, but with differences between NO<sub>2</sub> and TSP in autumn, between NO<sub>2</sub> and CO in spring. Additional analyses without ozone in the pollutant mixture are shown in Table 12-30. The principal values are not shown because they are quite similar to those in Table 12-27 except for the absence of component 2, representing ozone, and a corresponding increase in the principal value for component 3. The principal components of the four-pollutant mixture in Table 12-30 are quite similar from season to season. There is a primary component 1 in which all four pollutants are given similar weight, representing 65 to 72% of the non-ozone variance. This corresponds to overall high or low levels in all four pollutants, and is likely to be inversely related to wind speed. Component 2 largely reflects the differences between SO<sub>2</sub> (representing stationary sources) and CO (representing mobile sources) in all seasons, explaining 15 to 20% of the variance, with TSP making a relatively minor contribution to the SO<sub>2</sub> component loading. Component 3 largely represents the difference between TSP and SO<sub>2</sub> in all seasons, and explains 7 to 10% of the non-ozone pollutant variance in each season. Component 4 consists primarily of NO<sub>2</sub> in spring, summer, and winter; it appears to contrast NO<sub>2</sub> with TSP in the fall, and it explains 6 to 9% of the variance. Thus, it seems

**TABLE 12-29. PRINCIPAL COMPONENTS OF THE POLLUTANTS FOR  
PHILADELPHIA IN THE YEARS 1974-1988, BASED ON  
THE CORRELATION MATRICES IN TABLE 12-27**

Season		Component Loadings				
Spring	Pollutant	1	2	3	4	5
	TSP	0.803	0.363	0.006	-0.462	0.102
	SO <sub>2</sub>	0.773	0.203	-0.534	0.255	0.102
	O <sub>3</sub>	-0.058	0.923	0.315	0.209	0.039
	NO <sub>2</sub>	0.899	-0.067	0.155	0.075	-0.396
	CO	0.742	-0.451	0.387	0.159	0.266
Summer						
	TSP	0.822	0.112	0.117	-0.542	0.072
	SO <sub>2</sub>	0.771	0.146	0.472	0.315	0.251
	O <sub>3</sub>	0.506	0.676	-0.519	0.123	0.043
	NO <sub>2</sub>	0.845	-0.197	0.020	0.126	-0.481
	CO	0.546	-0.698	-0.391	0.062	0.242
Fall						
	TSP	0.894	0.184	-0.032	-0.292	0.284
	SO <sub>2</sub>	0.824	0.122	-0.490	0.259	-0.006
	O <sub>3</sub>	-0.000	0.963	0.235	0.128	0.005
	NO <sub>2</sub>	0.909	0.037	0.113	-0.155	-0.367
	CO	0.772	-0.387	0.427	0.246	0.109
Winter						
	TSP	0.836	0.361	-0.171	-0.358	0.113
	SO <sub>2</sub>	0.843	0.175	-0.365	0.345	0.075
	O <sub>3</sub>	-0.664	0.717	0.183	0.099	0.037
	NO <sub>2</sub>	0.901	0.054	0.156	0.002	-0.401
	CO	0.814	-0.027	0.530	0.088	0.219

Source: U.S. EPA calculations based on results reported by Samet et al., 1996a.

that TSP effects can be substantially distinguished from those of NO<sub>2</sub> (except possibly in the autumn) and can be reasonably distinguished from those of CO in all seasons. O<sub>3</sub> may be a potential confounder in summer, but not otherwise. The most consistent potential confounder

**TABLE 12-30. PRINCIPAL COMPONENTS OF FOUR POLLUTANTS FOR  
PHILADELPHIA IN THE YEARS 1974-1988, BASED ON  
THE CORRELATION MATRICES IN TABLE 12-27, EXCLUDING OZONE**

Season		Component Loadings			
Spring	Pollutant	1	2	3	4
	TSP	0.810	-0.331	0.464	0.139
	SO <sub>2</sub>	0.776	-0.444	-0.439	0.091
	NO <sub>2</sub>	0.899	0.167	0.018	-0.405
	CO	0.734	0.629	-0.070	0.246
Summer					
	TSP	0.810	0.245	-0.521	0.112
	SO <sub>2</sub>	0.771	0.435	0.396	0.254
	NO <sub>2</sub>	0.864	-0.084	0.102	-0.486
	CO	0.608	-0.758	0.048	0.230
Fall					
	TSP	0.894	0.160	0.301	0.291
	SO <sub>2</sub>	0.824	0.443	-0.355	-0.011
	NO <sub>2</sub>	0.909	-0.054	0.195	-0.364
	CO	0.772	-0.595	-0.200	0.103
Winter					
	TSP	0.869	0.279	0.402	0.072
	SO <sub>2</sub>	0.852	0.377	-0.344	0.119
	NO <sub>2</sub>	0.906	-0.149	-0.043	-0.391
	CO	0.818	-0.523	-0.021	0.237

Source: Samet et al., 1996a.

for TSP is SO<sub>2</sub>, but even here, the collinearity is not so severe as to discourage further analyses. It would therefore seem possible that a structured approach to evaluating copollutant interrelationships would allow construction of more realistic TSP exposure indices than simply using the mean of TSP, SO<sub>2</sub>, NO<sub>2</sub>, and CO. A conceptual basis for modelling discussed in Section 12.6.3.5 illustrates what these data suggest, i.e., that NO<sub>2</sub> and SO<sub>2</sub> are primary pollutants and that TSP is partly a secondary pollutant - including components generated from SO<sub>2</sub> and NO<sub>2</sub>. The analyses by Samet et al. (1996a) represent a first step in this direction.

A more direct assessment of potential confounders is based on simply evaluating the stability of the TSP effect or other pollutant effects when other pollutants are included in the model. This is, in many contexts, among the least biased of all confounder selection methods (Mickey and Greenland, 1989). A review of Table 12-26 shows that the TSP effect changes by more than 10% from a base value of 1.06 (Model 3) when  $O_3$  is *not* included as a covariate, and when  $SO_2$ ,  $NO_2$ , CO, or LCO are included (Models 4, 8, 9, 10). The TSP effect is: reduced by 30% when  $SO_2$  is included; reduced by 10% when  $O_3$  is included; increased by 14% when LCO is included; increased by 35% when CO is included (although the CO effect is *negative*); and increased by 70% when  $NO_2$  is included (although the  $NO_2$  effect is significantly *negative*, more likely indicative of collinearity than a beneficial health effect from  $NO_2$  exposure). The  $SO_2$  effect is more sensitive to the inclusion of TSP, a 44% reduction, than is the TSP effect to inclusion of  $SO_2$ . There is also a smaller increase of the  $SO_2$  effect when  $NO_2$  or CO are included. The  $O_3$  and LCO effects are nearly invariant, suggesting that they may be important covariates, but not confounders of TSP or  $SO_2$  effects. We cannot assess the effects of models that include  $O_3$ , LCO, and some combination of two or more pollutants including TSP. In particular, the effects of  $O_3$  and LCO on the simultaneous estimates of TSP and  $SO_2$  would be of interest.

Cifuentes and Lave (1996) also evaluated additive linear models using combinations of TSP,  $SO_2$ , and  $O_3$ , but with results for the years 1983 to 1988 that differ somewhat from those derived by Moolgavkar et al. (1995b). The results are summarized in Table 12-31 for each season and for the whole year, showing all combinations in which at least one pollutant was used to fit the total mortality time series. The time series were adjusted for weather and for time trends. The most consistently predictive pollutant in these models is TSP. Model 1, with all three pollutants, shows a significant TSP effect for spring and for autumn, with smaller effects that are not quite statistically significant at the 0.05 level for summer and winter.  $SO_2$  effects are positive only in winter, but not significant. Model 2 shows similar results without including  $O_3$ , with a somewhat larger and statistically significant effect for TSP in summer. When TSP is the only pollutant used as a predictor of mortality in Model 3, it is similar in magnitude and statistically significant in all seasons. When  $SO_2$  is used

**TABLE 12-31. RELATIVE RISKS OF TOTAL NON-EXTERNAL MORTALITY FOR ADDITIVE LINEAR MODELS  
USING TSP, SO<sub>2</sub>, AND O<sub>3</sub> IN PHILADELPHIA, 1983 TO 1988. INCREMENTS ARE 100 µg/m<sup>3</sup> FOR TSP,  
100 µg/m<sup>3</sup> FOR SO<sub>2</sub>, 100 ppb FOR O<sub>3</sub>**

Season	Model						
	1	2	3	4	5	6	7
	TSP	TSP	TSP	---	TSP	---	---
	SO <sub>2</sub>	SO <sub>2</sub>	---	SO <sub>2</sub>	---	SO <sub>2</sub>	---
	O <sub>3</sub>	---	---	---	0	O <sub>3</sub>	O <sub>3</sub>
Spring	TSP	1.090 <sup>1</sup>	1.080 <sup>1</sup>	---	1.078 <sup>1</sup>	---	---
	SO <sub>2</sub>	0.960	---	1.036	---	1.012	---
	O <sub>3</sub>	---	---	---	1.005	1.039	1.041
Summer	TSP	1.088	1.081 <sup>1</sup>	---	1.074 <sup>1</sup>	---	1 <sup>1</sup>
	SO <sub>2</sub>	0.984	---	1.067	---	1.027	---
	O <sub>3</sub>	---	---	---	1.010	1.037	1.040
Autumn	TSP	1.114 <sup>1</sup>	1.093 <sup>1</sup>	---	1.076 <sup>1</sup>	---	---
	SO <sub>2</sub>	0.977	---	1.050	---	1.044	---
	O <sub>3</sub>	---	---	---	1.130	1.184 <sup>1</sup>	1.160 <sup>1</sup>
Winter	TSP	1.050	1.081	---	1.095 <sup>1</sup>	---	---
	SO <sub>2</sub>	1.039	---	1.064	---	1.079 <sup>1</sup>	1 <sup>1</sup>
	O <sub>3</sub>	---	---	---	1.094	1.115	1.081
All Year	TSP	1.088 <sup>1</sup>	1.093 <sup>1</sup>	---	1.082 <sup>1</sup>	---	---
	SO <sub>2</sub>	1.008	---	1.058	---	1.052 <sup>1</sup>	1 <sup>1</sup>
	O <sub>3</sub>	---	---	---	1.031	1.045 <sup>1</sup>	1.050 <sup>1</sup>

<sup>1</sup>95% Confidence Interval > 1.

Source: Cifuentes and Lave (1996) Tables 6 and 7.

alone in Model 4, it is statistically significant only in winter. The TSP effect is nearly the same in Model 5 when  $O_3$  is also used as a covariate, suggesting little confounding between  $O_3$  and TSP.

### ***Concentration-Response Models with Piecewise Linear Components***

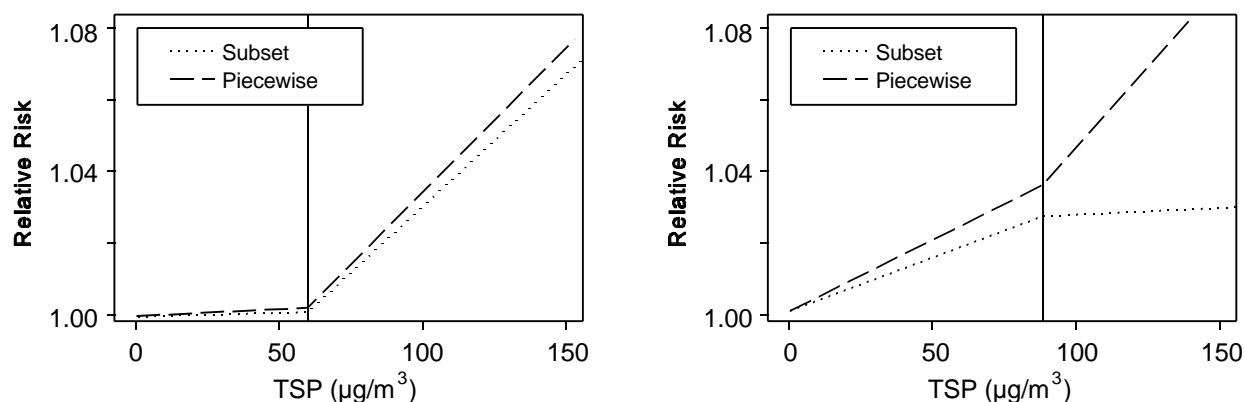
Cifuentes and Lave (1996) have evaluated several important classes of alternatives to the log-linear Poisson models fitted by other investigators, using Philadelphia TSP data for 1983-1988 in which both daily  $SO_2$  and ozone data were also available. Their results are shown in two forms in the paper: (1) restriction to subsets of data below a given level of TSP; (2) piecewise linear models with specified values of the joint point  $c$ . The results for the latter are shown in their Table 10 and Figure 4. These models fit in the more general form:

$$s(PM) = a \text{ PM} \quad \text{if } PM < c,$$

$$s(PM) = b (PM - c) + d \quad \text{if } PM > c.$$

A continuous piecewise linear function or linear spline has  $d = ac$ , and a discontinuous function has  $d \neq ac$ . The subset and piecewise continuous functions for  $c = 59 \mu g/m^3$  (the 50th percentile of TSP) and for  $c = 91 \mu g/m^3$  (the 90th percentile of TSP) are shown in Figure 12-32. For the subset of analyses using same-day TSP values the apparent statistical significance of the estimated RR shows a slight decrease with decreasing sample size as the cutoff concentration  $c$  (not necessarily a concentration at which the two linear segments intersect) decreases to  $100 \mu g/m^3$ .

The results for continuous piecewise linear models are shown in Figure 4 of Cifuentes and Lave (1996). The upper half of the the piecewise linear relationship is consistently high (RR of 1.04 to 1.08 for all cut points  $c = 30$  to  $90 \mu g/m^3$ ), and is statistically significant except for the small number of data points above  $90 \mu g/m^3$ . The lower half of the piecewise linear model also shows a strong relationship to TSP (RR of 1.047 to 1.055) for TSP at cut points of  $90 \mu g/m^3$  or above, with general statistical significance. There is little relationship in the lower part of the piecewise linear fit for cutpoints between 30 and  $60 \mu g/m^3$ . This suggests that there are some substantial deviations from a purely linear additive models involving TSP and certain covariates or copollutants at TSP levels below  $100 \mu g/m^3$ , but that the deviations are not necessarily indicative of a “threshold” model with slope 0



**Figure 12-32. Relative risk of death versus total suspended particles (TSP) level for each of the models used to explore the threshold levels, for disease deaths. The model includes SO<sub>2</sub> and O<sub>3</sub>, as well as control for weather using the full specification. The breakpoints are at 59 µg/m<sup>3</sup>, the 50th percentile of TSP, and at 91 µg/m<sup>3</sup>, the 90th percentile of TSP.**

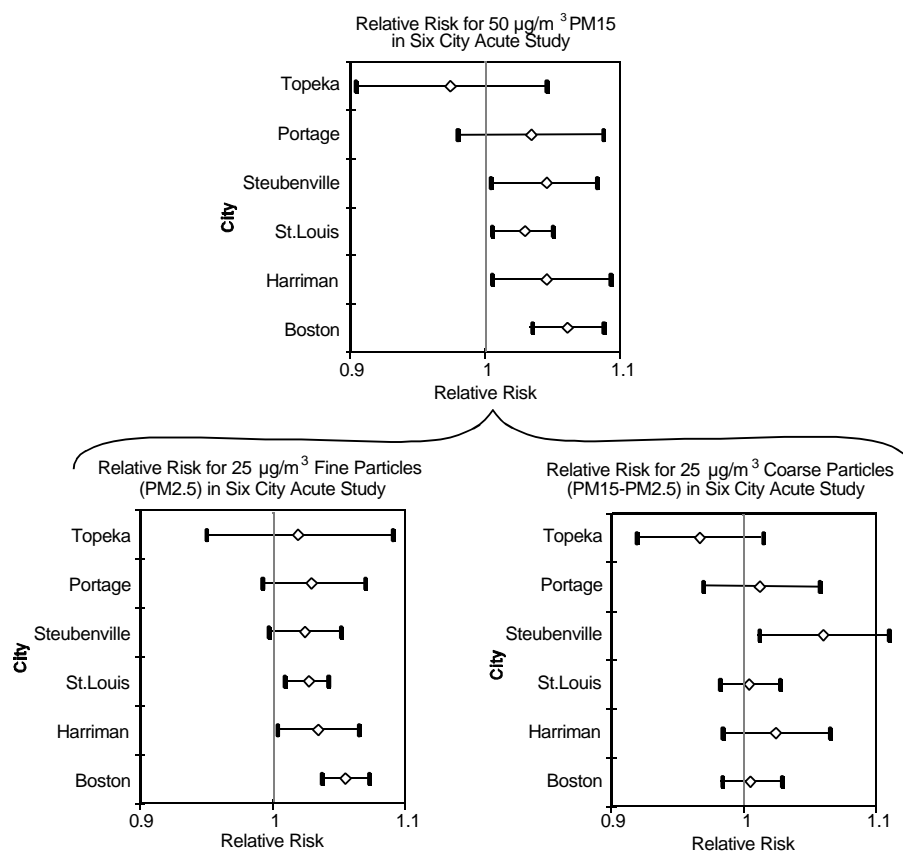
Source: Cifuentes and Lave (1996).

(RR = 1.00) below some cutoff level  $c$  as shown in Figure 12-32. While Cifuentes and Lave show the results of fitting a nonparametric loess smooth model of temperature and dewpoint, there is no analogous nonparametric model for TSP shown in the paper.

The HEI study (Samet et al., 1995) largely confirmed the additive linear model estimates derived by other investigators, and so will not be shown here. A major new finding from this study is that the marginal mortality-pollution curves for TSP and the two-dimensional smooth response surfaces fitted to mortality data using both of these pollutants was significantly nonlinear and nonadditive. This is discussed below in evaluating copollutant models.

### ***Model Specification Using Fine Versus Coarse Versus Thoracic Particle Indices***

The recent reanalyses of the Six City Study by Schwartz et al. (1996) allow evaluation of the effects of thoracic particles (PM<sub>15</sub>), fine particles (FP = PM<sub>2.5</sub>), or coarse particles (CP = PM<sub>15</sub> - PM<sub>2.5</sub>) as exposure indices. The reported results were transformed to standard increments of 50 µg/m<sup>3</sup> PM<sub>15</sub>, 25 µg/m<sup>3</sup> PM<sub>2.5</sub>, and 25 µg/m<sup>3</sup> for CP, as shown in Figure 12-33.



**Figure 12-33. Relative risks of acute mortality in the Six City Study, for inhalable particles (PM<sub>10</sub>, PM<sub>15</sub>), fine particles (PM<sub>2.5</sub>) and coarse particles (PM<sub>15</sub>-PM<sub>2.5</sub>).**

Source: U.S. EPA graphical depiction of results from Schwartz et al. (1996).

It is clear that, across the six cities, PM<sub>2.5</sub> is the most predictive of the three PM indices except in Steubenville, where a more significant CP effect was found (although the FP effect size for Steubenville was nearly as large as in most other cities). In spite of very considerable differences among the cities in terms of climate and demographics, the FP effect sizes were rather consistent. The CP effect sizes were positive, small, and not significant except for Steubenville (positive, significant) and Topeka (negative, nearly significant). Since PM<sub>15</sub> was the sum of FP and CP, it had an intermediate significance, with positive and significant effects except for Portage and Topeka. The St. Louis and Harriman/Knoxville associations for PM<sub>15</sub> and FP were both significant, possibly because of the use of nonparametric smoothers to adjust for weather and time trends. Overall, the pattern of results obtained most strongly implicates fine particles (PM<sub>2.5</sub>) as

contributing to PM-mortality relationships in the subject six cities. The Steubenville results suggest that, in some cases, CP may also need to be considered as well as FP in evaluating PM health risks.

### ***Model Specification for Other Mortality Studies***

Other studies on acute mortality have evaluated alternative model specifications. A number of OLS and time series regression models for COH in Santa Clara were compared by Fairley (1990). Mortality studies for Detroit (Schwartz 1991a) and Birmingham (Schwartz, 1993a) evaluated other regression and time series approaches. These are not reported in as much detail as the studies cited here, and the Detroit study also uses estimates for PM. Lipfert and Wyzga (1995a,b) also compare many of the above mortality studies using elasticity as a risk index.

### **12.6.2.2 Model Specification for Morbidity Studies**

There have been a large number of recent studies on hospital admissions related to PM (Schwartz, 1993b, 1994b, 1994e, 1995a, 1995b, 1996). These have used generally similar strategies for evaluating alternative Poisson regression models. The basic model includes a set of variables for temperature and dewpoint (usually in 6 to 8 categories), linear and quadratic time trends, indicators or dummies for each month in each year (so that no assumptions need to be made about recurrent seasonal or monthly effects), and the PM indicator. Alternative model specifications usually include: (1) piecewise cubic spline functions for time trend, temperature, and dewpoint; (2) generalized additive models (GAM) for time trend, temperature, and dewpoint; (3) basic model, excluding all non-attainment days ( $PM_{10} > 150 \text{ ug/m}^3$ , or ozone  $> 120 \text{ ppb}$ , etc.); (4) basic model without hot days; (5) extended range of lag times or moving averages; (6) basic model plus co-pollutants. Differences in RR for PM among most specifications is small. RR estimates from the GAM method tend to be higher than most other specifications, but the conclusions about RR are fairly insensitive to alternative specifications. Since there have been no studies that disagree with these conclusions, these are not reviewed below in detail, since the assessments are in many ways similar to those for the acute mortality studies.

### **12.6.2.3 Model Specification Issues: Conclusions**

Published research articles have provided a substantial amount of evidence about the consequences of different model specifications for short-term and long-term models. The short-term studies have been generally consistent across many different kinds of model specifications. The general concordance of PM effects, particularly in analyses of short-term mortality studies, is a consequence of certain appropriate choices in modelling strategy that most authors have adopted, but the results are not dictated by the use or misuse of any specific model. While it is conceivable that different plausible model specifications could lead to markedly different conclusions, this has not emerged thus far.

### **12.6.3 Other Methodological Issues for Epidemiology Studies**

The issues in air pollution epidemiology for PM are similar to those of many other pollutants. No single air pollutant, nor any mixture such as PM or an identifiable component of PM, is uniquely related to a specific health outcome. Also, in the PM studies individual exposure measurements are generally lacking, with exposure to PM typically measured at only one site in an urban or regional airshed or, at most, at a few widely spaced sites. U.S. studies of acute mortality typically depend on combining three data bases: (1) mortality data tapes provided by the National Center for Health Statistics (NCHS); (2) air pollution data sets for urban areas, accessed through the Aerometric Information Retrieval System (AIRS) network; and (3) meteorological data for urban areas and smaller SMSA's, obtained from the National Climatic Data Center (NCDC). Hospital admissions data involve a more diverse set of sources. Merging the data sets has not always been a straight-forward task, and attempts to replicate results have sometimes been complicated by the fact that different investigators have used different approaches to creating a merged data set for subsequent analyses. As a simple example, the  $PM_{10}$  monitoring data for Chicago consists of every-day monitoring at one site and every-6-days monitoring at up to eight other sites. In that case, different investigators may calculate different  $PM_{10}$  concentrations according to how the data from the intermittent monitoring sites are combined with data from the every-day site. In this section, specific methodology issues encountered in the studies reviewed earlier are discussed.

### 12.6.3.1 Particulate Matter Exposure Characterization

PM<sub>10</sub> measures the inhalable particles better than TSP. The U.S. EPA NAAQS are specified by PM<sub>10</sub> concentrations, which were not generally available before 1986. PM<sub>10</sub> is also a better index of ambient fine particle exposure than TSP because it is more uniformly distributed in an urban area or region than TSP. Since fine particles from outside can also penetrate indoors and constitute a major fraction of indoor air concentrations, PM<sub>10</sub> is also likely to be a better index of indoor air exposure to ambient fine particles than TSP. Currently, PM data on AIRS do not allow discrimination among important components of PM<sub>10</sub>, including fine particles, coarse particles, or sulfates. In the absence of any clearly demonstrated mechanistic relationship between PM components (by size, composition, or source) and specific health endpoints, there is little a-priori reason to believe that health endpoints related to PM should not be predicted well in different studies by different PM indices. The indices include PM<sub>10</sub>, fine particles (defined as PM<sub>2.5</sub>), coarse fraction of PM<sub>10</sub> particles (defined as PM<sub>10</sub> - PM<sub>2.5</sub>), or surrogates (e.g., sulfates, SO<sub>2</sub>, or H<sup>+</sup>) that may be more closely correlated with fine particles than to coarse particles. Results presented by Dockery and Pope (1994b) suggest that PM<sub>2.5</sub> may be a more appropriate "proxy" of exposure to particles that are predictive of health effects. This has also been generally supported by Schwartz et al. (1996), although there appears fully to be some situations, such as in Steubenville, where coarse particles cannot be ruled out as contributing to observed PM-health effects relationships.

PM<sub>2.5</sub> particles are more likely to be uniformly distributed within an urban airshed and, upon penetrating indoors, to be removed less rapidly from indoor air than coarse particles, so that outdoor ambient fine particle concentration becomes a better predictor of total fine particle exposure than ambient coarse particle concentration does for total coarse particle exposure. However, it is not clear that inhalable coarse particle fractions (i.e., PM<sub>10</sub>-PM<sub>2.5</sub>) can be entirely discounted in terms of their potential health effects. While sulfates are a significant part of fine particle levels in some places, they may be of more limited value as an indicator of a toxic component of PM<sub>10</sub> due to measurement artifacts (filter artifacts). The usefulness of sulfate data may also be limited because of regional and seasonal differences of sulfate levels. Information on other components of PM<sub>10</sub>, including acidity, metal ions, and organic components, is often not available. Similarly, data deficiencies exist for most co-pollutants. In studies where SO<sub>2</sub> is a good proxy for PM<sub>10</sub>, it may be difficult to assign effects to one or the other without evaluating the relationships linking the two, since SO<sub>2</sub> is the source of some fraction of particle sulfates.

Chapter 7 on Human Exposure to PM indicates that variations in ambient PM concentration can be significantly correlated, on a longitudinal (day-to-day) basis, with the variation of individual personal PM exposures as measured by personal monitors. However, cross-sectional correlations of individual exposures with ambient PM concentrations are typically low. In terms of community air pollution, a properly sited ambient PM measurement is reasonably related to the mean personal PM exposure of the community, and on a time series basis it may be a good indicator of the variability of any single individuals' daily PM exposure. An important consideration here is that the ambient monitors be properly sited in relation to the populations they are intended to represent. This would have to be evaluated study by study, which can be difficult or impossible if pertinent data were not been reported for the study. There must be limits to the acceptability to using a monitor for daily level changes in regards to both the distance from the population and the terrain between the population and the monitoring site (e.g., a mountain range).

Data are available at more than one monitoring site in a few studies, including Birmingham AL (Schwartz, 1993a, 1994e), Utah Valley (Pope et al., 1992, 1994), Los Angeles (Kinney et al., 1995; Kinney and Ozkaynak, 1991), San Francisco Bay area (Fairley, 1994), Philadelphia (Wilson and Suh, 1995), and Chicago (Ito et al., 1993, 1995; Styer et al., 1995). While  $PM_{10}$  varies from place to place, with a decreasing correlation with increasing distance across a metropolitan area, measurements are well correlated up to a few kilometers (Burton et al., 1996). Fine particle measures (e.g.,  $PM_{2.5}$  and sulfate) are particularly well correlated across a metropolitan region.

### ***Exposure Relevance***

The majority of the PM data used in the PM/mortality literature are daily observations, rather than the standard every-6th-day observations. The ambient daily mean PM levels reported in these PM/mortality studies of U.S. cities range from  $28 \mu g/m^3$  (St. Louis, MO) to  $58 \mu g/m^3$  (Los Angeles, CA) for  $PM_{10}$ ;  $76 \mu g/m^3$  (Cincinnati, OH) to  $111 \mu g/m^3$  (Steubenville, OH) for TSP. Other PM indices in the literature include CoH (monthly mean range = 9 to 12) in Santa Clara County, CA; and KM (mean = 25) in Los Angeles County, CA. The data description reported for these PM indices indicate a generally skewed distribution, and the maximum daily values deviate about 50 to  $150 \mu g/m^3$  from these means. The current 24-h NAAQS,  $150 \mu g/m^3$ , is rarely exceeded in these communities. Many of these communities studied were urban, but the

PM levels observed appeared to be representative of metropolitan areas where substantial fractions of the U.S. population reside.

### ***Size and Chemistries***

In theory, since TSP includes particle sizes ( $d_a < 50 \mu\text{m}$ ) that exceed those having thoracic deposition ( $d_a < 10 \mu\text{m}$ ), it is expected that TSP would be a less reliable measure of particulate matter for health effects analyses. However, comparison of the significance of the PM regression coefficients in the recent U.S. PM/mortality studies do not show systematically lower significance for TSP than  $\text{PM}_{10}$ . This may be because, so long as TSP levels fluctuate together with smaller particles over time, TSP may still be a reasonable surrogate for thoracic or fine particles, albeit not as good as  $\text{PM}_{10}$ . The error introduced by large particles depends on their local availability and, therefore, it is site-specific.

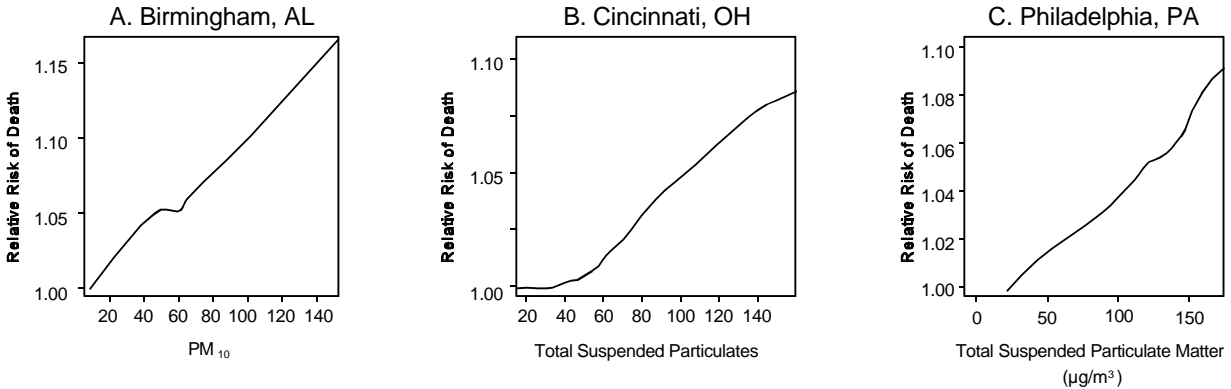
In most of the PM/mortality time series studies, only one PM index was employed. An exception is the study conducted in St. Louis, Mo. and Kingston, TN (Dockery et al., 1992). In this study,  $\text{PM}_{10}$ ,  $\text{PM}_{2.5}$ , sulfates, and aerosol acidity were available. The regression results indicate that, for both cities,  $\text{PM}_{10}$  showed the most significant mortality associations, and the significance declined as the size of the index decreased. However, the sample size of this study was relatively small ( $n = 300$ ;  $\text{PM}_{10}$  coefficient t-ratio = 2.17 in St. Louis, and 1.07 in Kingston), and the sample size for the aerosol acidity was even smaller ( $n = 200$ ). Furthermore, we currently do not know the extent to which the measurement errors of these different PM measures affect PM/mortality significance. Thus, it is as yet premature to relate the significance of various PM measures to size or chemistry specific causality from this study. Cross-sectional studies reported more significant mortality associations for fine particles ( $\text{PM}_{2.5}$ ; Dockery et al., 1993; sulfates: Ozkaynak and Thurston, 1987). However, significant PM/mortality associations have also been reported in areas where summertime sulfates are not the major component of PM (e.g., winter analysis of Santa Clara, CA; Los Angeles, CA). All the PM measures in the U.S. studies do include some type of combustion source originated particles (e.g., automobile emissions in Los Angeles, sulfates in the eastern U.S.). Overall, PM composition varies widely, not only between sites, but also over time at a single site. This represents a major challenge to any attempts to quantify PM-related health impacts.

### 12.6.3.2 Exposure-Response Functions, Including Thresholds

A PM threshold for mortality is difficult to detect because of small numbers of deaths (especially when broken down by age group and cause of death), and because the observed PM concentration is only a surrogate for exposure. In general, the threshold question has not been extensively examined except by Cifuentes and Lave (1996). Even in their analyses, there is no precise estimate of a change point in the relationship, with values of TSP in the range of 60 to 90  $\mu\text{g}/\text{m}^3$  as possible cutpoints. Other model specification issues that have had little examination include non-linear transformations of pollutant variables, interactions among pollutant variables, and interactions between meteorological variables and pollutants.

#### *Thresholds*

Many of the recent U.S. PM/mortality studies have reported PM/mortality "exposure-response" curves of the data, after controlling for weather and seasonal variables (Schwartz, 1993a, 1994a; Schwartz and Dockery, 1992a; Pope et al., 1992). Measurement error is a limiting factor in the ability to detect thresholds, no matter what methods are used. Some of the smoothed curves are shown in Figure 12-34. Some estimates were constructed by using quintile or quartile indicator variables in the regression, or by nonparametric smoothing (in the Generalized Additive Models), both of which should allow for possible non-linear relationships. In all the figures presented, a generally monotonic increase in mortality, as PM increases, is suggested. However, a search for a threshold from these results is difficult because of the distribution of the available number of datapoints. For example, in the plots of the quintile (or quartile) PM versus relative risk, the resolution of the shape of slope is determined by the number (5 or 4) of indicator categories. The lowest quintile (or quartile) could be higher than a potential threshold level (e.g., the lowest quintile of TSP was about 50  $\mu\text{g}/\text{m}^3$  in Philadelphia), or other discontinuities might be present at some higher level if finer level breakdown of the data were feasible. However, because estimation of more stable



**Figure 12-34. Smoothed nonparametric estimate of relative risk of mortality in three studies, where the particulate matter index is either total suspended particulates or  $PM_{10}$ , in micrograms per cubic meter.**

Source: A. Schwartz (1993a), B. Schwartz (1994a), C. Schwartz and Dockery (1992a).

coefficients requires greater numbers of cases, even a large dataset may not allow smaller data division than quintiles. Thus, from these results, we cannot determine if any threshold exists below approximately  $50 \mu g/m^3$  for TSP or  $20 \mu g/m^3$  for  $PM_{10}$  or if other discontinuities exist in the range of the observed data. Samet et al. (1995) derived quintile estimates for many of the studies cited here; but the quintile estimates derived by Samet et al. (1995) were based on the observed PM values in each study, whereas those derived by Schwartz and by Pope were based on adjusted PM values on weather and time.

Nonparametric smoothing of relative risk versus PM can, in theory, allow greater resolution of the shape. However, the stability of the results also depends on the weights of neighborhood and the interval of the PM, or "span", used to compute each segment of the curve (these parameters are not described in the relevant publications). Again, these smoothed curves, as with the quintile approach, cannot describe the shape of the curve where data do not exist. For example, the smoothed curve shown in Figure 12-34 for Cincinnati, OH, appears to suggest a threshold around  $40 \mu g/m^3$  of TSP, but the distribution (25th percentile TSP =  $53 \mu g/m^3$ ) indicates that there are not enough data points below  $40 \mu g/m^3$  to obtain stable curve shape below this level. Lack of data densities and confidence intervals makes any detailed examination more difficult. Thus, while these figures do collectively suggest a linear-like PM/mortality relationship,

any examination of a threshold level is limited by the data. Most other studies did not consider or present graphical examination of the possible shape of any exposure/response relationship and, thus, the results could have been constrained by the functional form specified in the regression model.

Samet et al. (1995) exhibits smooth nonparametric concentration-response functions for TSP and SO<sub>2</sub> (Figure 11 in their report), for all ages, ages < 65, and 65+. For all ages mortality and over 65 mortality, there appears to be a piecewise linear response which increases only for TSP > 100 µg/m<sup>3</sup> (all ages) or TSP > 60 µg/m<sup>3</sup> (age 65+). The SO<sub>2</sub> relationship is quadratic. However, the nonparametric smooth response surface for TSP and SO<sub>2</sub> differs significantly from this simple threshold model.

#### **12.6.3.3 Adjustments for Seasonality, Time Lags, and Correlation Structure**

Trends, long-term and medium-term recurrent or cyclical effects, and effects of medium-term non-recurrent or random events such as influenza epidemics are removed from the data so that short-term responses to short-term changes in PM concentration can be detected without confounding or interference from longer-term effects. For Gaussian time series models, this can usually be done well by filtering. However, filtering has the potential to remove longer-term effects of PM exposure, and therefore may underestimate the true PM effect. For example, death may occur from PM exposure during the first few days after exposure because the PM exposure may exacerbate pulmonary insufficiency in individuals whose respiratory capacity has already been compromised, especially the elderly and the ill. This may also contribute to excess short-term cardiovascular mortality. However, if PM exposure also compromises the immune system, the exposed individual may succumb to an infectious disease some weeks after the PM exposure, an effect that would be more likely to be cancelled out by application of filtering or other detrending techniques. Detrending could also be done by using regressors that are functions of the time or day of study. Candidate regressors are Fourier series (sums of sine and cosine terms), polynomial functions of time, dummy variables for year, season or quarter, month, or day of week. Fourier series are mathematically convenient, but require many terms in order to fit asymmetric seasonal variations, and cannot include random year-to-year differences in seasonal effects. Dummy variables for year, season, and month provide a great deal of flexibility, but may still be too "rough" in that such models allow abrupt changes between December 31, 1980 and January 1,

1981, between June 30 and July 1, and so on. Non-parametric smoothers such as spline functions, LOESS smoothers, and generalized additive models are often good choices, but as with any other detrending procedure, the scale or span of the smooth detrender determines what medium-term effects are removed from the model.

A number of short-term studies have provided reasonable control over time-related exogenous changes. The use of tapered high-pass filters in Gaussian time series models, in connection with linear time trends or dummy variables for season or day of week, has been demonstrated in numerous papers, for example, among acute mortality studies: (Shumway et al., 1988; Schwartz and Marcus, 1990; Kinney and Ozkaynak, 1991; Ito et al., 1993; Thurston and Kinney, 1995; Kinney et al. 1995; Ito et al., 1995).

### ***Mortality Displacement***

It is possible that there is a causal effect of airborne PM, but rather than altering the long term average mortality rate, peaks in exposure simply advance the date of death of otherwise terminally ill subjects. The terms "mortality displacement" or "harvesting" have generally been applied to this hypothesis. Under this scenario, lowering particulate matter concentrations might grant a few extra days life to a small part of the population, but have no effect on the general mortality rate. It is obviously extremely important for policy making purposes to resolve whether this is indeed the case.

Although the possibility has been discussed in several of the papers reviewed (Lipfert and Wyzga, 1995a,b), only a few (Spix et al., 1993; Cifuentes and Lave, 1996) seem to have offered a serious test of the hypothesis. They point out that the effect of harvesting should be to induce a negative effect on the autocorrelation, since "a high number of deaths on one day may leave a smaller number of vulnerable individuals at risk of dying on succeeding days." They further suggest that the magnitude of this effect should be proportional to the excess deaths due to pollution. Hence, they test the hypothesis by adding an interaction between the pollutant level on that day and the last k days mortality deviation from the expected value, where the expected value is based on a previously fitted model including trend, season, and influenza epidemics. A negative estimate for this interaction term would be interpreted as evidence for this phenomenon. Applying this test to data from Erfurt, East Germany, Spix et al. found a weak effect for suspended particles in the expected direction (nominal one-tailed  $p = 0.07$  ignoring the multiple

testing for k): the RR comparing the 5th and 95th percentiles of the exposure distribution was 1.51 if the previous 18 days mortality was above expected, 1.26 if it was below expected. A somewhat similar approach, examining mortality displacement from summer heat waves, has been described by Kalkstein et al. (1994).

Cifuentes and Lave (1996) examined short-term mortality displacement in two different ways. One method was to look at mortality autocorrelation coefficients. Total mortality showed a negative correlation at lag 2 days, and deaths outside of hospital inpatients had negative autocorrelation for lags 1 and 2 days. This is consistent with depletion of a potentially susceptible population by acceleration of death by 1 or 2 days, but is not a strong demonstration of the hypothesis.

A much more detailed analysis was based on the definition of "episodes" by Cifuentes and Lave. Episodes are contiguous periods of time in which pollution levels tend to be relatively elevated. They identified more than 100 such 3-day "episodes" during the 6 year period. Positive residuals (excess mortality) during the episode and negative residuals after the episode suggest displacement of mortality during that episode. However, the number of deaths occurring after the episode was typically smaller than the number occurring during the episodes suggesting that some of the excess deaths occurring during the episode were not among people who were certain to die within a few days anyway. Different methods for estimating the number of deaths, for time lags etc., produce different estimates of short term displacement. Alternative explanations such as unusual weather events cannot account for the mortality deviations observed during that period of time. Additional analyses of this reported effect would be of great interest including evaluation of out-of-hospital deaths.

The estimates comparing the first day of a three-day episode and the first day after an episode are shown in Table 12-32, for three age groups (Cifuentes and Lave, 1996; Table 10). The mean residuals are based on the best fitted model, using TSP, SO<sub>2</sub>, and O<sub>3</sub>. The mean number of deaths is greater than predicted on the first day of the episode. For total mortality, the excess is 0.874 deaths against 1.98 predicted for the given TSP level, or an excess of  $0.874 / 1.98 = 44\%$ . For the first day after the episode, there is a deficit of 0.895 deaths less than the 1.68 expected at the smaller post-episode value of TSP, or a

**TABLE 12-32. MEAN OF TSP, MODEL RESIDUALS, AND PREDICTED AND OBSERVED DEATHS FOR THE FIRST DAY OF THE EPISODES AND THE FIRST DAY AFTER THE EPISODES, FOR THE THREE AGE GROUPS.**

Age Group	Period	n	Avg. TSP ( $\mu\text{g}/\text{m}^3$ )	Mean of Residuals (deaths/day)	Daily Deaths		
					Predicted (deaths/day)	Observed (deaths/day)	Res./predicted
All							
	Episode	109	71.9	0.874	1.98	2.85	0.44
	After	109	61.3	-0.895	1.68	0.78	0.53
Age 18-64 years							
	Episode	82	70.5	0.642	0.73	1.38	0.87
	After	82	65.7	-0.591	0.68	0.09	0.87
Age 65+ years							
	Episode	120	73.7	0.759	1.61	2.37	0.47
	After	120	62.0	-0.503	1.35	0.85	0.37

Source: Cifuentes and Lave (1996).

deficiency of  $0.895 / 1.68 = 53\%$ . There is a large effect in adults of ages 18 to 64 years, with an 87% excess during the first day of a three-day episode and an 87% deficiency in the first day after the episode. The effect for older adults is also large, with a 47% excess during the episode and 37% fewer deaths than expected in the first day after the episode. This strongly suggests that some of the individuals who would have otherwise been expected to die on the first day after the episode may have died 3 days prematurely, on the first day of the episode.

One should also be quite clear about what Table 12-32 does *not* show. The effect of an episode in causing premature deaths is focussed primarily on deaths that occurred within a day or two after exposure, but does not preclude premature deaths that may have occurred more than two days after exposure. There is no estimate here of the cumulative excess of episode-related deaths that were displaced by more than a few days. While acute responses following exposure suggests a cause-effect relationship with at least some short-term displacement of mortality, the

question of long-term excess mortality over times greater than a few days must be addressed by the long-term mortality studies.

The statistical properties of this test merit further research. However, a full investigation of the performance of the test in realistic settings with the more sophisticated time series and GEE methods, including estimation of the harvesting parameter  $k$  is beyond the scope of this assessment.

In addition to statistical research, further epidemiologic research is warranted to better characterize the excess deaths in terms of age, cause of death, hospitalization status, prior morbidity, etc. It may be necessary to develop a multistage model, with recruitment of individuals from a healthy stage through one or more stages of morbidity until they reach a susceptible stage at which acute air pollution exposure may cause deaths.

There is, at present, relatively little basis for quantifying the shortening of life in some individuals by periods of months or years using time series data.

#### **12.6.3.4 Adjustments for Meteorological Variables and Other Confounders**

There has been only limited progress in developing a systematic approach to the use of weather-related variables in daily mortality or morbidity studies. A variety of ad hoc procedures have been used. While various statistical methods for adjusting daily mortality or morbidity time series for weather effects appear to be successful on a case-by-case basis, there is little understanding of how to do this systematically in a way that appropriately characterizes current knowledge about the relationship between weather, weather changes, and changes in mortality. The empirical adjustments used in most studies are made with little theoretical basis and may be arguable for that reason alone. It is clear that the effects of some variables, such as temperature, are intrinsically nonlinear, and that it may be more useful to define the likelihood of excess weather-related mortality by the presence of clusters of related meteorological variables, such as the synoptic classes suggested by Kalkstein et al. (1994) and used by Pope and Kalkstein (1996) for the Utah Valley. While the synoptic class approach appears promising, it has so far been applied to relatively few cities, and may require further modification to be applicable in a general health effects modelling framework. The problem is that meteorological variables are confounded with other pollutants as well as with PM, so that any misspecifications of the relationship between health effects and weather can provide a distorted set of residual effects to be modelled using air

pollution variables. A causal or mechanistic model could be useful in relating weather, season, pollutant emissions, pollutant concentrations, behavior as it affects exposure, and health endpoints. Remarkably, weather continues to be significantly related to mortality and other health effects, in spite of increasing use of air conditioning.

One interesting possibility in the use of synoptic categories has been demonstrated by Kalkstein et al. (1994). They showed that during the most offensive synoptic weather category, there may be little detectable relationship between PM and excess mortality since most of the excess is attributable to weather. During non-offensive weather categories, however, the excess mortality attributable to PM is readily detected since the weather effect is much smaller and there is a quantitative dose-response relationship between PM and excess mortality.

Weather/climate control between studies has been discussed by Schwartz (1994a,b), Dockery and Pope (1994b) and others as a qualitative issue rather than as a formal numerical evaluation. These papers present global comparisons of RR between cities studied that are labeled as warm or cold cities, based on longer term mean temperature. Since the actual study analysis looked at day to day changes, long-term comparisons of means may not be as informative or appropriate to examine in such a global manner. First, it is not clear that the classification of a city as a warm or cold climate is correct. This dichotomy does not consider moderate climates in a continuum as a factor, so the comparison may not be appropriate. Second, the mortality in the studies is examined on a daily basis as is the temperature. Mean comparison over several months of temperature is an inappropriate control for the study design.

### ***Interrelationships Between Weather, PM, and Mortality***

A number of studies have concluded that both extreme weather and high pollution adversely affect mortality. While a majority of this research has examined the independent effect of these stresses on mortality, few studies have successfully separated weather-induced from pollution-induced mortality. This has been especially true in the evaluation of acute mortality. There have been some efforts to evaluate these differential impacts (e.g., Ramlow and Kuller, 1990; Shumway et al., 1988; Schwartz and Dockery, 1992a,b).

Some authors have conducted weather/pollution/mortality evaluations in Steubenville, OH; Philadelphia, PA; London, England; Birmingham, AL; and Utah County, UT as well as other locales. In all of these investigations, they have reported significant associations between human

mortality and PM, and in some cases, the relationship extends to levels well below the current National Ambient Air Quality Standard. In several, they have also alluded to a weather-mortality relationship. For Steubenville, a positive non-linear relationship between both temperature and dew point temperature and mortality was detected. When dummy variables were used to denote hot days, humid days, and hot/humid days, the hot/humid days were a significant predictor of mortality. When seasonal variations were controlled for in their Poisson regression models however, neither temperature nor dew point proved to be significant predictors of mortality (Schwartz and Dockery, 1992b). In a study of British Smoke in London, Schwartz and Marcus (1990) controlled for temperature and humidity and improved the model results significantly over the results of a model with no meteorological variables.

More recent studies indicate that controls for weather may probably not have been adequate to determine true meteorological impacts in the evaluations cited above. Many PM/mortality studies utilize rank-ordered temperatures, squared temperature and dewpoint values, moving averages of temperature, and mean temperatures for groupings of days (see Table 12-33 for further details), which may not provide the detail to detect true weather/mortality relationships. In addition, it is probably not feasible to assume that cities within a wide range of climates demonstrate similar weather/PM impacts on mortality, and there are possibly some regional similarities in response which have not been adequately explored. In a reanalysis of Philadelphia mortality/PM relationships, Schwartz (1994b,c) took a more direct approach to examine the possibility of confounding weather impacts. The reanalysis utilized Hastie and Tibshirani's (1990) "Generalized Additive Model" to detect and control for nonlinearities in the dependence of daily mortality on weather; nevertheless, this study uncovered findings similar to the original Philadelphia study. In addition, Moolgavkar et al. (1995a) assert that the role of weather was improperly evaluated within the Steubenville study, and suggest a more sophisticated evaluation of meteorology in future PM/mortality analyses.

**TABLE 12-33. ADJUSTMENTS FOR METEOROLOGICAL FACTORS IN SOME RECENT STUDIES RELATING MORTALITY TO PARTICULATE MATTER**

Location Studied and Authors	Pollution Data and Treatment	Mortality Data and Treatment	Weather Data and Treatment	Pollution/Weather Impact
<u>London</u>  Schwartz and Marcus (1990)	British Smoke measurements from 7 stations; logarithmic and square root transformations;	Daily total death counts, including respiratory and cardiovascular causes; sensitivity to filtering	Temperature and RH; grouped plots of temperature and humidity versus mortality; autoregressive model.	British Smoke is significant predictor of mortality; temp/humidity control increased significance, as did autocorrelation adjustment
<u>Philadelphia</u>  Schwartz and Dockery (1992a)	TSP samples collected routinely at two monitors; supplemented by sampling every sixth day at several sites; daily means and lags used	Daily total, elderly, <65, pulmonary disease, pneumonia, cardiovascular and cancer mortality; Poisson regression using GEE;	Mean 24 h temp and DP including squared transformation; indicator variables for season, hot, cold, humid, and hot humid days, and year.	Significant TSP association mortality, strongest among elderly and respiratory patients; hot days, mean DP, other weather factors also associated
<u>Steubenville</u>  Schwartz and Dockery (1992b)	TSP from one monitor; ranked by levels and sorted into quartiles;	Daily total mortality; Poisson and weather model regressions;	Mean 24 h temp and DP; year as random effect; indicator variables for hot, humid, and hot humid days;	Nonlinear association between TSP and daily mortality; hot humid days associated with daily total mortality;
<u>Utah</u>  Pope et al. (1992)	PM <sub>10</sub> level from one site; up to 7-day lagged moving averages; divided into quintiles used as dummy variables;	Daily total, non-accidental respiratory, cardiovascular, and all other causes of non-accidental mortality; Poisson regression;	Temp and RH; dummy variables used for 10 °F ranges, previous day's temp, 5-day temp moving average, and humidity; linear time trend, random year effect;	Relative risk of death increased monotonically with the mean PM <sub>10</sub> level for each quintile; also observed when weather controlled;
<u>Erfurt, East Germany</u> Spix et al. (1993)	Suspended particulates; 0-3 day lags; logarithmic transformation;	Daily total mortality; Poisson regression; autocorrelation adjustment for "harvesting"	Daily mean temp, RH, precipitation; indicator variables used for very cold days and hot days for different thresholds, various lags;	Effects of air pollution smaller than influenza and weather effect; significant SO <sub>2</sub>
<u>Birmingham</u> Schwartz (1993a)	PM <sub>10</sub> level averaged from all (1-2) city monitors; divided into quartiles used as dummy variables;	Daily total mortality; Poisson regression using GEE; dummy variables for year and day of week; biannual cycle filters;	Mean 24 h temp and DP; dummy variables same as Utah study, plus cold days; 3-day moving lags;	Significant association between PM <sub>10</sub> and daily mortality; extremely hot weather also associated with excess mortality; relation to temperature.
<u>Steubenville</u> Moolgavkar et al. (1995a)	TSP from one monitor and SO <sub>2</sub> (two series)	Daily total non-accidental mortality; Poisson regression; with and without GEE; full year and season; serial correlation unimportant.	Mean 24 h temp and DP; indicator variable for hot and humid days; temperature quintiles;	TSP influence on mortality greatly reduced when SO <sub>2</sub> included in analysis; choice of SO <sub>2</sub> series and season had large impact on mortality results.
<u>Philadelphia</u> Wyzga and Lipfert (1995b)	24 h averages of O <sub>3</sub> and TSP from several city monitors; lags of 0 to 4 days tested	Daily non-accidental deaths (non-elderly and elderly); linear filtering; variable for time over entire period in stepwise regression and forced OLS.	Daily maximum temp.; daily change in barometric pressure; dummy variables for winter and seasonality	Strong relationship between temp. and mortality; seasonal adjustments very important; TSP-temp. interaction; most mortality with TSP on hot days.

To further control for weather, Schwartz (1994b,c) stated that the similar responses to air pollution in the "mild" weather of Philadelphia (based on a mean daily temperature of 57 °F) and "cold" weather of London reduce the confounding role of weather. Furthermore, Schwartz (1994b,c) notes that similarity in temperature and humidity on high and low air pollution days

(when different mortality response are noted) "... also would seem to eliminate weather as a potential confounder." However, it is possible that these studies do not remove the total confounding influence of weather, especially because of their dependence on mean temperatures and other meteorological surrogate which may not truly reflect weather variation.

There have been other studies which have attempted to assess the differential impact of PM and weather on acute mortality. For example, Ostro (1993) summarized studies which show strong associations between exposures to PM<sub>10</sub> and total daily mortality for many urban areas in the United States, Europe, and Canada. In addition, he notes that results are remarkably consistent across regions. However, the impact of weather as a confounding influence is implicitly considered rather unimportant. Ito et al. (1993) showed that daily mortality in London was significantly associated with aerosol acidity levels and British Smoke. Weather played a lesser role, and Ito's work confirms results obtained by others who have evaluated London's mortality/PM/weather relationship (Schwartz and Marcus, 1990; Thurston et al., 1989; Mazumdar et al., 1982). However, it should be noted that London's marine climate is rather benign when compared to many large American cities, as thermal extremes are unusual.

Some studies for cities exhibiting higher climate variation yielded somewhat different results. Wyzga (1978) used the Coefficient of Haze (COH) as a surrogate measure of PM concentration, and determined that high COH values are associated with increased mortality in Philadelphia. However, he recognized the potential impact of extreme weather as well, and noted that heat waves may also be responsible for large numbers of extra deaths. In a recent study by Wyzga in which weather was treated in a more sophisticated manner (Wyzga and Lipfert, 1995a), the impact of ozone concentrations and weather on acute mortality were evaluated and results were compared to TSP. The authors conclude that a determination of ozone and TSP impacts is most difficult because of the influence of confounders, particularly weather. In addition, use of different explanatory models yields disparate results, with pollution impacts ranging, "...from essentially no effect to response similar to that associated with a 10 °F increase in ambient temperature" (Wyzga and Lipfert, 1995a). This evaluation appeared to uncover a synergistic relationship between weather and pollution, as days with maximum temperatures exceeding 85 °F contributed most to the associations between TSP and mortality. Several other studies have uncovered synergistic relationships, and some of these consider pollution to be of secondary importance to weather in affecting acute mortality. Ramlow and

Kuller (1990) found that daily mortality was most closely associated with the daily average temperature of the previous day rather than any pollution measure in Allegheny County, PA. In a study which attempts to determine synergistic relationships between weather and pollution on mortality in Los Angeles, Shumway et al. (1988) determined that mortality is, "...an additive nonlinear function of temperature and pollution, whereas there may be significant interactions present, especially when low or high temperatures are combined with high pollution levels." The authors found that model-predicted average mortality values increased at both temperature extremes when particulate levels were held constant. Two evaluations in the Netherlands found temperature extremes in summer and winter to be primary determinants in mortality variation. Kunst et al. (1993) and Mackenbach et al. (1993) determined that the relationship between temperature and mortality is linear, producing a U-shaped temperature curve, with minimum mortality rates observed between 10 to 15 °C. The Kunst evaluation determined that summer acute mortality is not influenced by variations in air pollution concentration.

Although weather seems to induce mortality increases when temperatures are either very warm or very cold, the impact of weather as a confounder varies seasonally. For example, the impact of weather on acute mortality in winter is much more difficult to evaluate, and thermal relationships are decidedly weaker.

### ***Controlling for Weather in PM/Mortality Analyses: The Use of Synoptic Climatological Methods***

A number of procedures have been utilized to control for weather in PM/mortality studies, and although the variety has been great, they generally suffer from common shortcomings. First, many depend on arbitrary decisions to remove extreme weather events from the dataset. The definition of extreme weather to include, for example, days above 90 °F may be proper for a city in the north, but not for a locale further south. Thus, these arbitrary delineations consider weather as an absolute, rather than a relative, factor affecting human health. It is therefore possible that some stressful weather days are not identified, contaminating a PM/mortality dataset which is considered controlled for weather. Second, the use of weather "dummy variables" to control for meteorology within PM/mortality analyses categorizes weather within groupings which may not duplicate meteorological reality. Kalkstein et al. (1991, 1994) propose that the meteorology of a locale is defined by discrete, identifiable situations, which represent frequency modes for

combinations of weather elements. Meteorological delineation that recognize the existence of such modes can be used to control for weather within this context. Third, the use of mean weather elements (e.g., mean daily temperature) does not permit a proper evaluation of, or control for, daily weather extremes. Finally, most all consideration of weather in PM/mortality studies are thermal (temperature), and, less frequently, moisture (humidity) dependent. This creates a potential weather control problem, as certain meteorological phenomena, such as stormy situations associated with mid-latitude cyclones, are not associated with thermal extremes, yet may be very important contributors to acute mortality (Kalkstein et al., 1994). These are rarely controlled for in PM/mortality studies, as they cannot be identified on the basis of temperature and humidity.

A completely different approach is that adjustment for weather-related variables is needed only insofar as it provides a basis for removing potential confounding of excess mortality with PM and other air pollutants, and that any empirical adjustment for weather is adequate. One of the most completely empirical methods for adjusting daily time series data for covariates is by use of nonparametric functions, such as LOESS smoothers, generalized splines, or generalized additive models (GAM), as demonstrated in Schwartz (1994d,e,f,g,h; 1995a,b); and Schwartz and Morris (1995). These are empirically satisfactory and may provide a better fit to data than synoptic categories, but at the loss of a basis for defining weather "episodes" as a characterization of duration of exposure.

Application of synoptic climatological procedures to control for weather has the potential to compensate for these difficulties and add further insight by defining an entire set of meteorological conditions which lead to increases in mortality. Many U.S. cities tend to be especially affected by a single type of "offensive" summer air mass associated with unusually high mortality (e.g., Philadelphia, Table 12-34). This "moist tropical" air mass in

**TABLE 12-34. MEANS AND STANDARD DEVIATION FOR SUMMER AIR MASSES IN PHILADELPHIA**

Air Mass Category Number	Mean 3 PM Temperature	Total Mortality				Elderly Mortality			
		Mean Mortality <sup>a</sup>	Standard Deviation	% of Top 50 Mortality <sup>b</sup>	% Top 50 Frequency	Mean Mortality	Standard Deviation	% of Top 50 Mortality	% Top 50 Frequency
1	77.0	-4.11	12.87	2.00	0.14	-0.91	9.99	0.00	0.00
2 <sup>d</sup>	89.0	8.89	16.14	46.00	3.77	6.72	12.58	46.0	3.79
3	82.4	1.63	12.82	14.00	1.27	1.59	10.76	14.00	1.28
4	79.0	-4.43	10.19	0.00	0.00	-2.82	9.33	2.00	0.23
5	82.6	-2.57	11.14	4.00	0.45	-1.36	11.10	4.00	0.45
6	85.0	3.92	16.83	14.00	1.99	3.84	13.77	10.00	1.42
7	80.6	0.70	11.82	2.00	0.14	0.52	10.41	4.00	0.67
8	85.5	2.47	12.49	8.00	1.08	2.70	9.88	10.00	1.33
9	74.7	-4.49	12.53	0.00	0.00	-2.56	10.39	2.00	0.31
10	83.6	0.13	11.80	6.00	1.07	1.28	10.86	4.00	0.67

<sup>a</sup>Values are evaluated against a baseline of 0.

<sup>b</sup>Represents the percentage of top 50 mortality days within a particular synoptic category.

<sup>c</sup>Ratio of percentage of top 50 days within the synoptic category over the seasonal frequency of the category. A number greater than one indicates that a larger proportion of days in the synoptic category are among the top 50 mortality days than might be expected based on the frequency of the category.

<sup>d</sup>"Offensive" category.

Source: Kalkstein (1993).

Philadelphia, possessing the highest maximum and minimum temperatures, was also associated with the greatest standard deviation in mortality of all air masses evaluated. Thus, although many days within the offensive air mass were associated with high mortality totals, a number of days showed little mortality increase. The greatest daily mortality totals during moist tropical air mass incursions occurred as part of a lengthy string of consecutive days of the air mass, and when minimum temperatures were particularly high. This type of information may be important when controlling for weather in PM/mortality analysis.

Offensive air masses which lead to mortality totals significantly higher than the long-term baseline have been identified for a number of U.S. cities (Table 12-35). In most cases moist tropical air masses were deemed offensive (especially in the East), but the very oppressive "dry tropical" air mass was often associated with the greatest increases in mortality, especially in New York, St. Louis, Philadelphia, and in southwestern cities (Kalkstein, 1993b). In some cases, daily mortality totals are over 50% above the baseline (World Health Organization, 1996). The air mass analyses support the notion that acute mortality increases only after a meteorological threshold is exceeded. This threshold is not only temperature dependent; it represents an overall meteorological situation which is highly stressful. It is noteworthy that most cities demonstrate only one or two offensive air masses which possesses meteorological characteristics exceeding this threshold.

In a PM study where stressful weather days are removed from the data base, synoptic categorization provides an efficient means to remove such days with greater security that very few meteorologically offensive days are contaminating the remaining dataset. In studies where weather is stratified based on certain meteorological elements, synoptic categorization allows for a meteorologically realistic control, and may be preferable to the use of arbitrary dummy variables when identifying meteorological conditions with an elevated mortality risk.

### **The Effect of Different Weather and Time Trend Model Specifications on Concentration-Response Models for PM<sub>10</sub>**

A recent study by Pope and Kalkstein (1996) allows detailed assessment of the effects of the substantially different approaches to modeling concentration-response and weather variables. The original analyses and reanalyses of the Utah Valley data by Samet et al. (1995) use quintiles of

PM<sub>10</sub> as the indicator. The reanalyses reported by Pope and Kalkstein as Models 1-8 used a linear model for 5-day moving average PM<sub>10</sub>, and

**TABLE 12-35. DAILY EXCESSIVE MORTALITY (SUMMER SEASON) DURING  
OFFENSIVE AIR MASSES**

City	Offensive Air Mass	Mortality Above Baseline <sup>a</sup>	City	Offensive Air Mass	Mortality Above Baseline <sup>a</sup>
Birmingham	MT	+2	Kansas City	DT	+5
Phoenix	MT	+1		MT*	+3
Los Angeles	MT	+9	St.Louis	DT	+15
	DM	+3		MT*	+2
Riverside	DT	+2	Newark	DT	+6
San Francisco	DT	+9		MT*	+4
Hartford	MT	+3	Buffalo	MT*	+3
Tampa	MM	+1	Nassau, NY	DT	+6
	MT*	+3		MT*	+5
Atlanta	DP	+4	New York	DT	+49
	MT*	+3		MT*	+30
Chicago	DT	+9	Cincinnati	MT*	+2
	MT*	+14	Columbus	MT*	+3
Indianapolis	MT*	+3	Portland	DT	+5
Louisville	MT*	+2	Philadelphia	DT	+32
Boston	MT*	+8		MT*	+10
Baltimore	MT*	+5	Providence	MT*	+7
Detroit	DT	+10	Memphis	DT	+3
	MT	+8		MT*	+1
Minneapolis	DT	+4	Dallas-	DT	+3
	MT*	+6	Ft.Worth		
			Houston	DT	+8
			San Antonio	DT	+1

<sup>a</sup>Mean daily deaths above the long-term baseline.

Air Mass Abbreviations: MT = Moist Tropical; DM = Dry Temperate; DT = Dry Tropical; MM = Moist Temperate; DP = Dry Polar. Asterisks denote a particularly offensive subset of MT.

Source: Kalkstein (1993b).

8 different weather models: (1) no adjustment; (2) indicator variables for 20 seasons (1985-1990); (3) indicators for 20 seasons, and indicators for quintiles of temperature and relative humidity; (4) indicators for 20 seasons, and indicators for 19 synoptic weather categories; (5) linear time trend, and indicators for 19 synoptic categories; (6) LOESS smooth of time (span = 10 percent of days); (7) LOESS smooths of time (span = 10 percent of days), temperature (span = 50 percent of days), and relative humidity (span = 50 percent of days); (8) LOESS smooth of time (10 percent of days), and indicator variables for 19 synoptic categories. The results are shown in Table 12-36. The results are relatively insensitive to the form of time trend and adjustment for weather

variables, with RR for 50  $\mu\text{g}/\text{m}^3$  increments in  $\text{PM}_{10}$  varying only from about 1.058 (Model 2) to 1.077 (Model 7) for total mortality, all of them statistically significant. The pulmonary mortality models are somewhat more sensitive to the form of the covariate adjustments, with RR for 50  $\mu\text{g}/\text{m}^3$  ranging from 1.132 (Model 6) to 1.221 (Model 7); Model 2 shows only a marginally significant  $\text{PM}_{10}$  coefficient, the others significant one-tailed (Models 3 and 4) or two-tailed. The cardiovascular mortality models have RR ranging from 1.076 (Models 3 and 7) to 1.116 (Model 1), with Model 3 one-tailed significant and all other models showing a significant  $\text{PM}_{10}$  effect on cardiovascular mortality. While the authors comment that other communities may show greater sensitivity to the statistical methods for adjusting for time trend and weather, the relative lack of sensitivity of the estimated  $\text{PM}_{10}$  effect over a very wide range of models is noteworthy.

Table 12-36 also shows subset models corresponding to Models 7 and 8. Cold season models called Models 9 and 11 by Pope and Kalkstein (1996, Table 4) consist of Models 7 and 8 respectively, limited to the months of October to March. Intra-seasonal differences are adjusted by LOESS smoothers of time, and daily weather variation either by LOESS smoothers of temperature and relative humidity (Model 9) or by indicators for synoptic categories. Total mortality is highly significant in either case (1.070 for Model 9 and 1.059 for Model 11). Pulmonary mortality is higher (1.145 for Model 9 and 1.120 for Model 11) and marginally significant. Cardiovascular mortality has  $\text{RR} = 1.062$  in Model 9 (not significant) but  $\text{RR} = 1.075$  (significant) in Model 11. The corresponding Models 10 and 12 for the warm season (April-September) shows higher RR effects for total and pulmonary mortality, but the effects are not at all statistically significant. The lower statistical significance may reflect the halving of the sample size in these data sets, since the effect size estimates must be similar to those obtained by averaging the whole-data analyses across the corresponding seasons, with cold season = fall + winter approximately, and warm season = spring + summer approximately.

Pope and Kalkstein (1996) also show four nonparametric smooth regression plots corresponding to Models 1, 6, 7, and 8, respectively. All of the models using a nonparametric regression for daily mortality on  $\text{PM}_{10}$  are approximately linear, showing

**TABLE 12-36. EFFECTS OF DIFFERENT MODELS FOR WEATHER AND TIME  
TRENDS ON MORTALITY IN UTAH VALLEY STUDY**

Model Identity	Time Model	Weather Model	Relative Risk for PM <sub>10</sub> 50 µg/m <sup>3</sup>		
			Total Mortality	Pulmonary Mortality	Cardiovascular Mortality
Base I	-	-	1.076 (1.044, 1.109)	1.198 (1.035, 1.386)	1.094 (1.019, 1.174)
Base II	-	-	1.083 (1.030, 1.139)	1.215 (1.049, 1.408)	1.094 (1.020, 1.174)
1	None	None	1.074 (1.032, 1.118)	1.185 (1.056, 1.331)	1.116 (1.054, 1.181)
2	20 seasons	None	1.058 (1.002, 1.118)	1.133 (0.963, 1.333)	1.081 (1.000, 1.169)
3	20 seasons	Quintile	1.062 (1.003, 1.124)	1.150 (0.972, 1.361)	1.076 (0.992, 1.167)
4	20 seasons	Synoptic	1.068 (1.009, 1.130)	1.169 (0.988, 1.382)	1.090 (1.005, 1.183)
5	Linear	Synoptic	1.068 (1.020, 1.118)	1.183 (1.032, 1.356)	1.100 (1.030, 1.175)
6	LOESS	None	1.059 (1.017, 1.102)	1.131 (1.006, 1.273)	1.085 (1.024, 1.150)
7	LOESS	LOESS	1.077 (1.028, 1.129)	1.221 (1.063, 1.402)	1.076 (1.006, 1.152)
8	LOESS	Synoptic	1.068 (1.021, 1.117)	1.166 (1.018, 1.335)	1.099 (1.029, 1.173)
9	Cold season, LOESS	LOESS	1.070 (1.015, 1.129)	1.145 (0.981, 1.337)	1.062 (0.984, 1.146)
10	Warm season, LOESS	LOESS	1.112 (0.918, 1.346)	1.529 (0.813, 2.877)	1.053 (0.789, 1.404)
11	Cold Season, LOESS	Synoptic	1.059 (1.009, 1.111)	1.120 (0.971, 1.291)	1.075 (1.003, 1.153)
12	Warm season, LOESS	Synoptic	1.091 (0.947, 1.258)	1.394 (0.794, 2.577)	1.024 (0.780, 1.343)

Source: Pope and Kalkstein (1996)

some suggestion of nonlinear structure between roughly 60 and 100  $\mu\text{g}/\text{m}^3$   $\text{PM}_{10}$ , but in no case suggesting a threshold or consistent flattening of the concentration-response relationship at any  $\text{PM}_{10}$  concentration. The authors note that a chi-squared test comparing each non-parametric regression model for  $\text{PM}_{10}$  with the corresponding linear model shows no statistically significant deviation from linearity.

Samet et al. (1996b) have recently published another study of different methods for estimating the modifying effects of different weather models on the relationship of TSP and  $\text{SO}_2$  to total mortality in Philadelphia from 1973 to 1980. The models included the original Schwartz and Dockery (1992a) weather specification, a nonparametric regression model, LOESS smoothing of temperature and dewpoint, and Kalkstein's Temporal Synoptic Index (TSI) or Spatial Synoptic Category (SSC) models. The first three methods allowed the weather model to be adjusted so as to provide an optimal prediction of mortality, whereas the latter two models were based completely on external criteria and the classification of days by SSC or TSI categories was not adjusted to improve prediction of mortality. The authors conclude the "... the association between air quality as measured by either TSP alone,  $\text{SO}_2$  alone, or TSP and  $\text{SO}_2$  together, cannot be explained by replacing the original Schwartz and Dockery weather model with either a nonparametric regression, LOESS, or by synoptic categories using either Kalkstein's TSI or SSC systems. In addition, there is little evidence in the Philadelphia total mortality data to support the hypothesis that the pollution effects are modified by the type of weather conditions as measured either by TSI or by strata created from the predicted weather-induced mortalities using the Dockery and Schwartz model or the LOESS model. ... We did not find variation of the effect of pollution across categories of weather." Their results are not shown here.

Additional studies systematically evaluating the differential effects of PM and other pollutants by weather category would be of interest. The Philadelphia study by Samet et al. (1996b) used only TSP and  $\text{SO}_2$ , whereas the Utah Valley study by Pope and Kalkstein (1996) did not look at the effects of weather as a modifier with other pollutants as well as  $\text{PM}_{10}$ .

### *Confounding by Epidemics*

Concern exists that the increased incidence of illness or mortality associated with changes in air pollution during the winter season may not indicate a causal relationship because of confounding influences of contagious illnesses epidemics. Infectious respiratory illness (e.g., the "flu") strongly influences mortality. An underlying or contributing cause for changes in air pollution or in contagious illness may be weather changes. Confounding due to epidemics may be adjusted statistically to some extent by use of filtering, but this is at best suitable for time series with a normally distributed response, and filtering of time series may perform better when there is some recurrent medium-to-long wave pattern to outbreaks of the disease in a given population. Without some recurrence pattern, filtering may only eliminate evidence of longer-term persistence of health effects related to air pollution. Close inspection of the time course of infectious respiratory illness outbreaks in populations reveals that outbreaks do not appear on a regular schedule from year to year (Henderson et al., 1979a,b; Murphy et al., 1981; Chapman et al., 1981; Denny et al., 1983). In any given year, a number of important respiratory pathogens may not appear at all in a given population. Thus, fixed-cycle curve-smoothing techniques may not accurately describe the time course of respiratory illness outbreaks in populations. Several investigators have subsequently used long-term nonparametric methods such as loess smoothers or generalized additive models (GAM) to adjust mortality series for aperiodic fluctuations that may include time-extended outbreaks of respiratory disease (Pope, 1994; Schwartz, 1994b,c, 1995b).

It is sometimes possible to evaluate the effect of epidemics on health outcome time series by comparison with adjacent communities. Pope (1991) evaluated the possible effect on hospital admissions of contagious illnesses such as influenza (which is known to cause a substantial number of deaths in the elderly) and respiratory syncytial virus (RSV, which affects a substantial number of children and is often mistakenly diagnosed as influenza). There was particular interest in the possibility that infectious diseases occurred more often during the winters when the Utah Valley steel mill was open, and less often during the winter when the steel mill was closed, purely by chance. Pope writes that "The few diagnoses where the agent of disease was specified limited opportunities to directly observe epidemics of any specific infectious agent. Bronchitis and asthma admissions for preschool-age children were more than twice as high in Utah Valley during periods when the mill was operating than when it was closed. The potential of highly localized

epidemics of contagious respiratory disease that were correlated coincidentally with the operation of the steel mill cannot be completely ruled out. If the association were strictly spurious, however, the same correlation would probably be observed in neighboring communities unaffected by the mill's pollution. Such correlations were not observed."

The ability to directly observe diagnosed cases of influenza or RSV would allow a direct adjustment of health outcome time series for community-wide incidence of occurrence of the disease, which could in turn be exacerbated by co-occurring air pollution. Some progress in obtaining data on outbreaks of influenza-like illnesses (ILI) may be possible using recently established data bases, such as the CDC volunteer physician surveillance network. Evidence exists that these 140 family physicians make good sentinels for epidemics of ILI (Buffington et al., 1993). Data are provided to CDC on a weekly basis, which seems appropriate to the level of filtering that may be needed to adjust daily time series of health outcomes and air pollution for co-occurring respiratory diseases.

### ***Confounding: Is It a Real Problem?***

In developing criteria for assessing epidemiologic studies, we have paid a great deal of attention to the potential confounding of PM effects on human health with the effects of other agents that are associated with PM. Confounding has both conceptual and technical aspects. We will first discuss some of the conceptual aspects.

There are three distinct options by which an analyst can deal with confounding in an epidemiology study: (1) control; (2) avoid; or (3) adjust by analysis. It is obviously preferable to control confounding by designing a study in such a way that all of the potential confounding effects are anticipated and avoided. If confounding is unavoidable, then all levels of the nominal causal agent (PM) and its confounding factors should be included in the study, preferably in a balanced design so as to simplify the analyses of the data. Since the PM studies are all observational studies, study design rarely allows a representative sampling of all levels of all factors. For example, in a city or region where there are large stationary sources that burn fossil fuels containing sulfur, both PM and SO<sub>2</sub> are likely to be high at the same time or low at the same time, being governed by similar patterns of generation and dispersion. Likewise, if mobile sources burning fossil fuel are the primary source of PM in a region, then PM during the summer is likely to be associated with some or all of the following factors: high temperatures, low wind speed,

high concentrations of ozone, CO, and airborne nitrates. Therefore, avoiding situations in which confounding occurs is not usually an option.

However, there are some situations in which certain kinds of confounding are minimized. One example occurred in the Utah Valley studies. During the year that the mill was closed due to a strike, PM emissions from the mill were greatly reduced, but not quite eliminated since the coke ovens were banked during the closure, and not shut down. The years before and after the closure were years with high PM<sub>10</sub> concentrations and typical weather. The year during the closure had generally typical seasonal weather, but much lower PM<sub>10</sub> levels. Hence, confounding between PM<sub>10</sub> and weather was relatively minimal during the study. Other studies by Pope et al. (1991) and Pope (1989) in surrounding counties showed little evidence of any change in the incidence of respiratory infections during the year of closure, so that confounding of winter health effects with epidemics of respiratory infection seems unlikely. Other pollutants were at low levels even when the mill was operating, particularly SO<sub>2</sub>. Summer levels of ozone were high enough to merit covariate adjustment, but had little effect on the estimated RR for various health effects of PM<sub>10</sub>.

In general, the potential for confounding of PM effects with the effects of other air pollutants is regionally distributed, with sulfates forming a higher percentage of particle mass in areas of the eastern U.S. and Canada, and nitrates a larger percentage than sulfates in the western U.S. and Canada. Thus, the potential for confounding with SO<sub>4</sub><sup>=</sup> and with SO<sub>2</sub> is greater in studies in eastern states, and the potential for confounding of PM effects with effects of NO<sub>x</sub>, and (presumably) with other air pollutants such as CO and O<sub>3</sub> that are generated largely by mobile sources, varies with location. Likewise, there is some confounding of health effects of PM with health effects from weather, since weather conditions may affect both generation of PM and its atmospheric dispersion (that is, concentration). For this reason, it may also be helpful to take a multi-city or multi-study perspective in comparing the effects of potential confounding variables on RR for PM.

Schwartz (1994c,d; 1995a,b) has emphasized a multi-study and multi-endpoint perspective from several points of view. We believe that comparisons of study results across different studies is very useful, but the approach still leaves some unresolved questions about confounding. For example, a completely factorial design controlling for effects of weather and co-pollutants might require finding studies in both "hot" and "cold" cities, in "wet" and "dry" cities, in cities with "high" SO<sub>2</sub> and "low" SO<sub>2</sub>, with "high" O<sub>3</sub> and "low" O<sub>3</sub>. Thus, even a simple factorial design

would require comparisons of at least  $2^4 = 16$  cities, counties or SMSA's. Since the variables used in describing the cities are numeric, combining the results would be more appropriately done using a "meta-regression" in the same sense as in the cross-sectional analyses done for the long-term exposure studies, rather than a "meta-analysis". Meta-analyses are discussed below. In general, there have not been enough reported studies to do this "meta-regression". There are also problems in defining levels of weather effects, since Kalkstein et al. (1994) have shown that thresholds for excess mortality from high temperatures are different in different cities. That is, a "high" temperature in Minneapolis-St. Paul or Seattle, may not have the same effect in Birmingham or Los Angeles, and that differences may depend on other weather variables and on climate conditions. This approach also shares another concern about population-based cross-sectional studies, that populations in different cities are demographically different in ways that affect population-based health outcomes. Even the measure of effect size that we have used for most of our comparisons, relative risk of health outcome for PM or other factors, is relative to a base rate for the health outcome that one would expect to differ somewhat among different populations in different cities.

Avoidance of confounding is also possible for some co-pollutants. Gaseous chemical compounds such as  $\text{SO}_2$ , CO, and  $\text{O}_3$  are likely to have very similar effects in different conditions, everything else (such as temperature and humidity) being equal. When levels of these pollutants are very low, such as  $\text{SO}_2$  in most western studies, there is virtually no chance that these pollutants have a causal effect on health endpoints such as mortality and hospital admissions. While such effects cannot be absolutely excluded, the fact that they are often found at levels very far below the NAAQS should control their contribution to some extent.

In spite of these concerns, the general similarity of RR estimates for acute mortality in different studies and the large differences in potential confounding variables among the studies, along with the similarity of RR to that found in studies where confounding effects seem relatively minimal, adds a great deal of credibility to the conclusion that the PM mortality effects are real, and similar in many locations, even if their magnitude is small and somewhat uncertain. This is not to say that there is no confounding with co-pollutants, particularly where pollutants such as  $\text{SO}_2$  are generated by the same process that generates PM. Differences in RR for hospital admissions are somewhat greater, possibly reflecting differences in demographic factors or regional differences in hospital admissions criteria, but for similar reasons these estimates are not

so seriously confounded in every study as to preclude concluding that, in some studies, there are real increases in hospital admissions rates for the elderly, and for certain classes of respiratory and cardiovascular conditions.

### ***Control of Confounding By Covariate Adjustment***

For most of the short-term studies, there is some unavoidable confounding with co-pollutants, with weather, and possibly with other medium-term and long-term events such as epidemics and seasons. Different model specifications of some studies in Section 12.3 were compared at length in Section 12.6.2. Weather variables and temporal variations over times longer than a few weeks can be adequately modeled using any of several approaches discussed above, such as polynomials, sinusoids, indicator variables for each month and year, indicators of synoptic climatological categories, nonparametric smoothers or generalized additive models, or high-pass filtering for Gaussian models. Careful examination of residuals for Poisson or Gaussian models have found that a large number of alternative models can provide regression residuals or Poisson expectations apart from air pollution variables that are independent of season, so that seasonal subsetting of time series data in short-term studies may not be necessary for adequately adjusted models. Sometimes, as in analyses of the London mortality series (U.S. Environmental Protection Agency, 1986a; Schwartz and Marcus, 1990), only seasonal monitoring data are available, but one should not make a virtue of necessity by subsetting time series, since statistical tests to detect PM effects of the magnitude currently observed in the U.S. require long series of data, roughly at least 800 values. Apart from this sample size requirement, different methods for adjusting for weather and time trends provided adequate levels of adjustment to control for these factors. In addition to controlling confounding with air pollution, it is also important to fit very good models for weather and time trends in time series data, however, so as to help reduce residual variability in daily response data to the limiting or irreducible Poisson minimum variance, which is equal to the expected number on that day.

#### **12.6.3.5 Adjustments for Co-pollutants**

Not all studies contain data on the major co-pollutants, and a wide variety of approaches has been used to assess the importance of these co-pollutants as predictors of health effects that compete with PM in terms of explanatory power. Studies in which no other co-pollutant is

assessed probably over-estimate the PM effect, but the use of a large number of more or less closely related pollutants to predict the health outcome almost guarantees that the statistical significance and size of the PM effect will be under-estimated. So far, few of these studies have used effective diagnostic techniques or alternative methods for dealing with correlated (e.g. multicollinear) predictor data.

Earlier discussion has indicated that other pollutants such as  $\text{SO}_2$  are factors that play a role in modifying the relationship between PM and mortality when they are incorporated into models examining these relationships such that the RR is usually smaller. Other pollutants such as  $\text{O}_3$  and CO also need to be considered. Indeed as more studies incorporate these other pollutants into the studies, concern for the role they play becomes more important. This applies to hospitalization studies where possible relationships with CO may be evident. The biological plausibility of CO and sudden death is established. The earlier major air pollution episode events in London involved relatively high levels of CO (Commins and Waller, 1967). Section 12.6.2 conducted an intense examination of the roles of copollutants with a focus on  $\text{SO}_2$  but also  $\text{O}_3$  and CO to determine what roles these copollutants play and what summary statements are possible to allow conclusions about PM effects to be stronger.

One of the more difficult problems in interpreting the analyses of the studies discussed here is that of separating the effects of several air pollutants. These pollutants are often fairly highly correlated, and the correlation is often causal, in that several pollutants may be emitted by the same mix of sources in a community, or that one pollutant is a precursor to another pollutant or to a component of that pollutant, such as the fractions of sulfates and nitrates in PM that are secondary pollutants formed from  $\text{SO}_2$  or  $\text{NO}_x$ . There have been a number of studies in which several different model specifications were tested, involving PM as the only air pollutant, versus PM and other pollutants used jointly in the model. In many studies, such as TSP in Philadelphia (Schwartz and Dockery, 1992a) there was little effect of  $\text{SO}_2$  on the RR for TSP, whereas other authors have found that  $\text{SO}_2$  appeared to modify the TSP effect in some seasons, using a similar approach and data set, but with less comprehensive adjustment for weather variables and time trends. There are two ways in multi-pollutant models can cause differences in interpretation from a single-pollutant model: (1) the correlation between PM and the other pollutant(s) is (are) sufficiently high that the effect or health outcome attributable is shared among the pollutants and the individual RR for any one pollutant may be seriously biased. Measurement error in pollutants

or other covariates may also bias the result, not necessarily towards the null, and the most poorly measured exposure covariate is usually the one that is driven towards no effect; (2) parameter variance estimates are seriously inflated among the entire group of nearly collinear covariates, increasing estimated standard errors and the width of the confidence intervals for the RR estimates and thereby also attenuating their apparent statistical significance.

Collinearity diagnostics have been developed for Gaussian OLS regression models (Belsley et al., 1980) and are implemented in most modern statistical programs. Analogous methods for Gaussian, logistic, or Poisson time series models are less well developed. Most programs allow calculation of the correlation coefficient between estimates of regression parameters (denoted B) based on the asymptotic covariance matrix. However, as noted in Table 12-5, correlation of the B's was given in only two out of ten studies relating acute mortality to PM<sub>10</sub>. Pollutants with similar patterns and effects can be identified by B-correlation values close to -1. Numeric diagnostics for confounding of co-pollutants could be easily included in reports of long-term studies, many of which use Gaussian OLS linear or nonlinear regression methods for which these diagnostics are readily calculated.

Some investigators have noted that similarity of PM regression coefficients in single- and multiple-pollutant models is sufficient to show that PM is not confounded with the other pollutants. This is not the whole story, since there is a possibility that the B coefficient or RR for PM is unchanged, but the confidence limits are much wider because of the variance inflation of the parameter estimate for collinear pollutants. When the RR estimate for PM is relatively unchanged and there is little increase in the width of the confidence interval, then one can say there is little evidence of confounding. This has been done in a number of analyses discussed in this section, for example in the Utah Valley mortality study as shown in Figure 12-21. The RR estimates for the summer season and the width of the confidence intervals for PM<sub>10</sub> are similar without ozone in the model, with daily average ozone, or with maximum daily one-hour ozone as the co-pollutant. The summer PM coefficient, with or without ozone, is similar to the winter value, when ozone levels were so low as to have little probable effect on mortality, which illustrates both covariate adjustment and confounder avoidance strategies in the same study.

There is some question about whether the confounding of certain co-pollutants such as PM and SO<sub>2</sub> should be regarded as true confounding when one pollutant is part of a causal pathway from pollution source to pollution monitor (Rothman, 1986). Our assessment of probable causal

pathways in a hypothetical multivariate model relating source emissions, weather, air pollution, and health outcomes is shown in Figure 12-35. This could serve as a framework for a statistical analysis in which the direct and indirect effects of air pollutants and other factors could be disentangled using substantive scientific hypotheses and data.

### **Concentration-Response Surfaces for Two or More Pollutants**

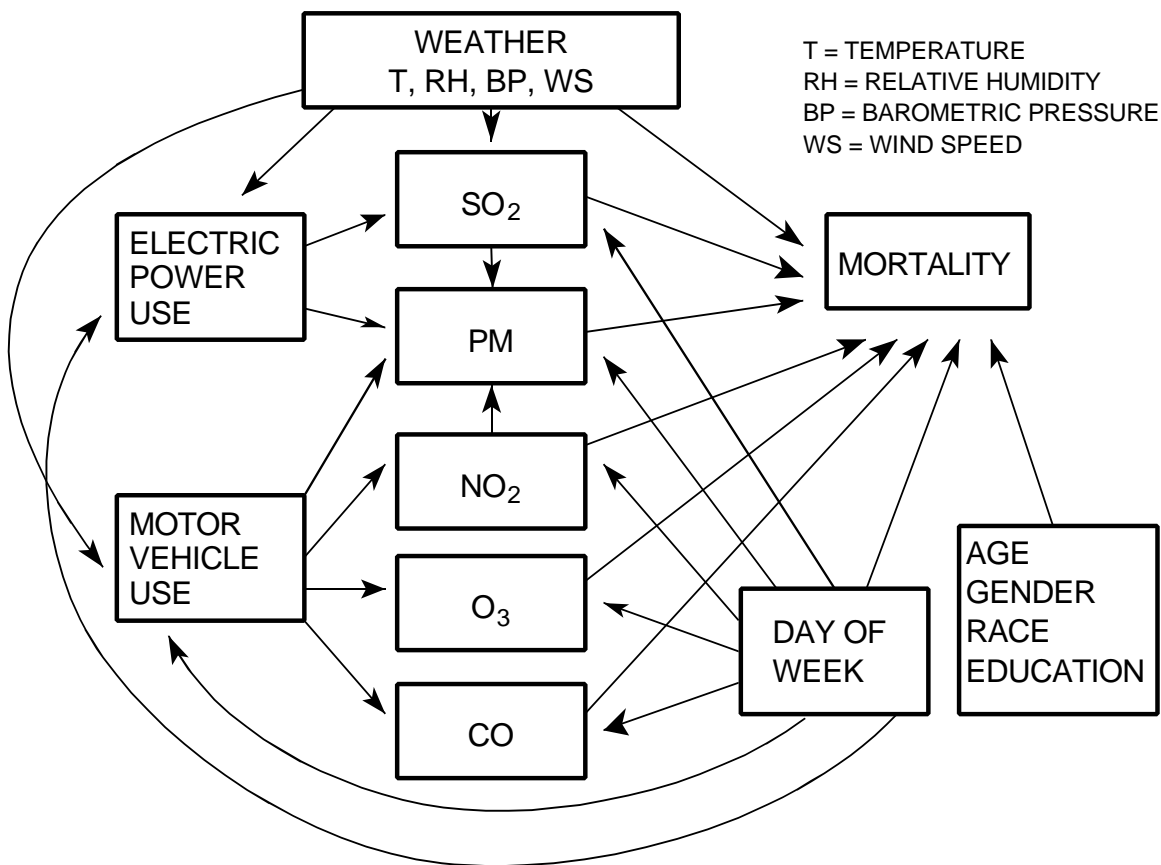
A recent study by the Health Effects Institute (Samet et al., 1995) shows how additive and interactive models can differ. An example of an additive linear model is one in which  $s(x) = bx$  and  $S(x) = dx$ , so that

$$\log(E(Y)) = XB + b \text{ PM} + d \text{ OP}$$

is constant along any line in which  $b \text{ PM} + d \text{ OP}$  is constant. When Samet et al. fitted a two-dimensional smoothing model to Philadelphia mortality counts against  $\text{PM} = \text{TSP}$  and  $\text{OP} = \text{SO}_2$ , where the general form of the model was defined by a two-dimensional nonparametric smoothing function  $ss$ ,

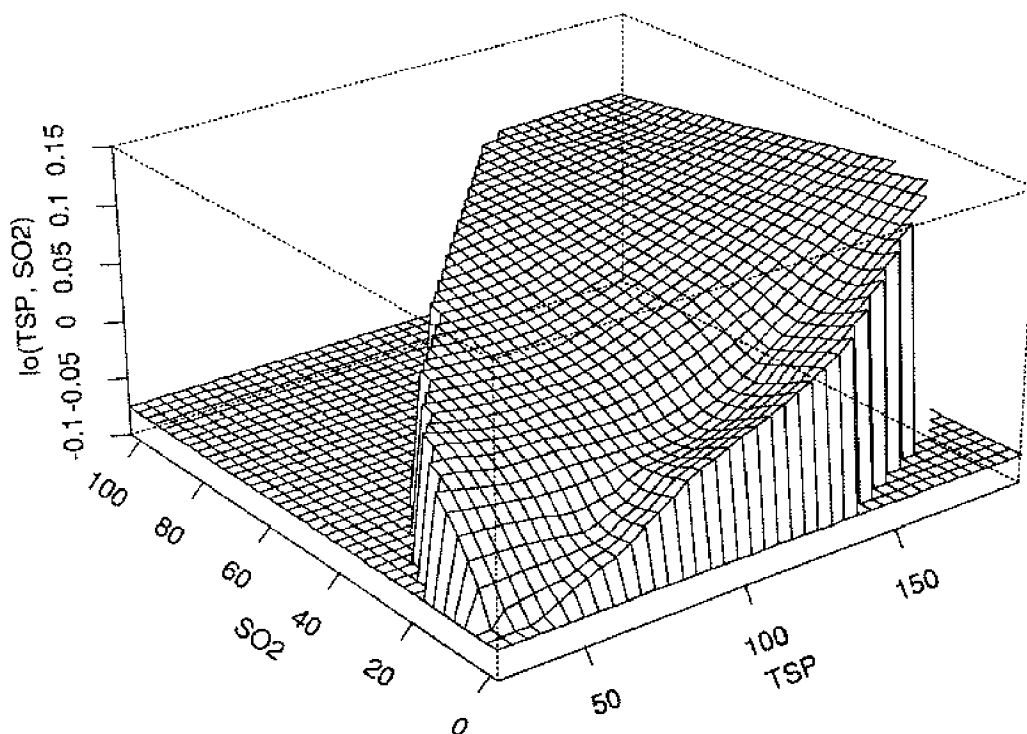
$$\log(E(Y)) = XB + ss(\text{TSP}, \text{SO}_2),$$

the resulting models differed substantially from an additive linear form and showed evidence of very strong non-linearity as well as non-additivity.



**Figure 12-35. A conceptual model of sources and pathways for air pollution health effects such as mortality, including a causal model of potential confounding by co-pollutants. No attempt is made to differentiate strength of evidence for each pathway.**

In general, most papers have provided very little empirical basis for the reader to assess the adequacy of the fitted model, especially for analyses involving copollutants. The most data-driven display would consist of a three-dimensional scatterplot, whose axes are the PM index, the copollutant, and the response variable (mortality). The HEI report comes closest to this by presenting three-dimensional surfaces showing the *smoothed* or fitted mortality response versus TSP and SO<sub>2</sub> for the 1973 to 1980 Philadelphia data set (see Figures 12-36 and 12-37). The smoothed surfaces are based on LOESS smoothers whose bandwidth includes 50 percent of the data, reflecting a substantial degree of smoothing of daily mortality counts. The smoothed actual data surface falls considerably above the linear model

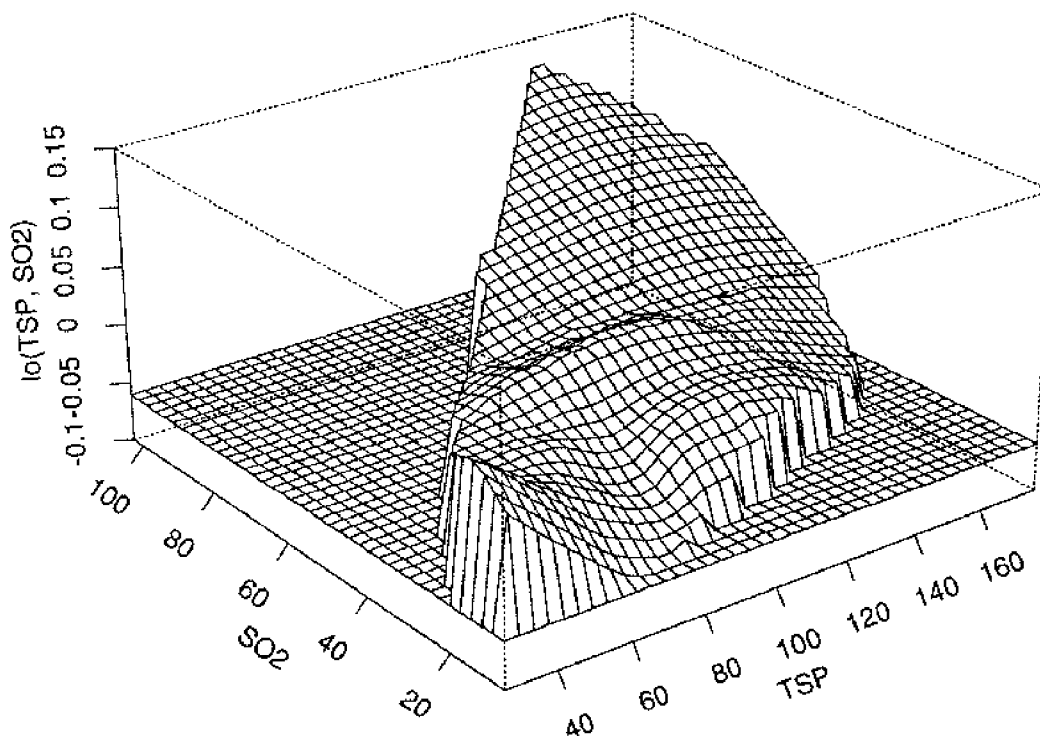


**Figure 12-36. Smooth surface depicting relative effects of sulfur dioxide ( $\text{SO}_2$ ) and total suspended particles (TSP) levels on total mortality for Philadelphia, 1983 to 1988. Surface was estimated from a generalized additive model (Hastie and Tibshirani, 1990) using a LOESS smoother (bandwidth 50% of data, 10.2 degrees of freedom). Deviations from a plane surface suggest a nonlinear concentration-response function.**

Source: Samet et al. (1995).

surface for TSP greater than about  $100 \mu\text{g}/\text{m}^3$  and almost all  $\text{SO}_2$  levels above 20 ppb. Below about  $75 \mu\text{g}/\text{m}^3$  TSP, the plane surface generally lies above the smoothed data surface. This suggests that there is a very complex pattern of dependence on the joint values of TSP and  $\text{SO}_2$  that is not adequately captured by an additive linear model.

A somewhat different way of looking at the results from Figure 12-36 is shown in Figure 12-38. Figure 12-38 shows the contours of the same two surfaces projected onto the plane with TSP and  $\text{SO}_2$  values for each day in the data set. The contour lines represent TSP and  $\text{SO}_2$  combinations for which the estimated excess risk of mortality in Philadelphia is equal to the value shown. The parallel lines are estimates from the regression plane in the additive linear model. The curved contours represent smoothed estimates from the LOESS



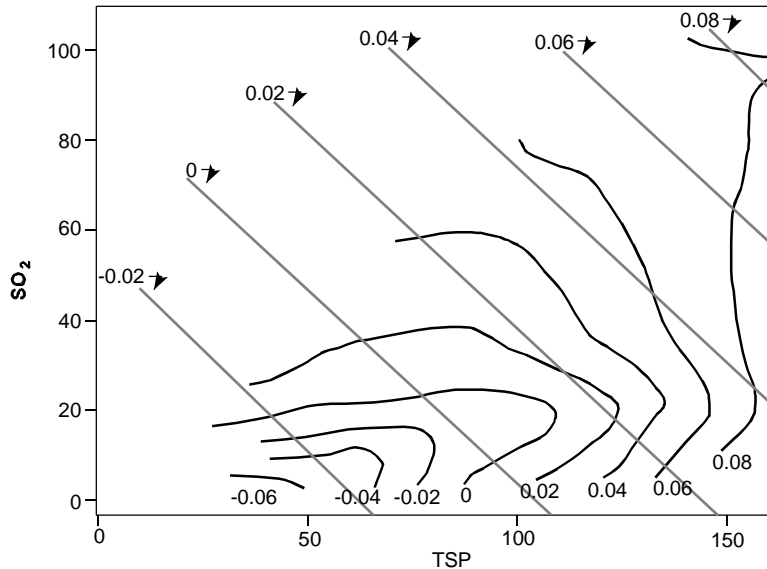
**Figure 12-37. Smooth surface depicting Philadelphia mortality in winter relative to sulfur dioxide ( $\text{SO}_2$ ) and total suspended particles (TSP), 1973 to 1980. Surface was estimated from a generalized additive model (Hastie and Tibshirani 1990) using a LOESS smoother with 9.6 equivalent degrees of freedom, controlling for temperature, dew point, and day of the week.**

Source: Samet et al. (1995).

smoothing model and may be thought of as simplified representations of the data. The two sets of curves appear quite different, and in fact the difference in deviance of the mortality counts between the LOESS model (with 10.2 equivalent degrees of freedom) and the additive linear model (with 2 degrees of freedom) is 28.0 with 8.2 degrees of freedom, which is a statistically significant difference at level  $P = 0.01$  after adjustment for overdispersion of the mortality counts (Samet et al., 1995, p. 31).

The nature of the nonlinear and nonadditive response surface provides additional information. If the contour lines in Figure 12-38 are roughly parallel to the horizontal axis (TSP), then the figure suggests that mortality is changing in relation to the variable on the vertical axis

(SO<sub>2</sub>), as is suggested for TSP less than about 75  $\mu\text{g}/\text{m}^3$ . If the contour lines in Figure 12-38 are roughly parallel to the vertical axis (SO<sub>2</sub>), then the figure suggests that



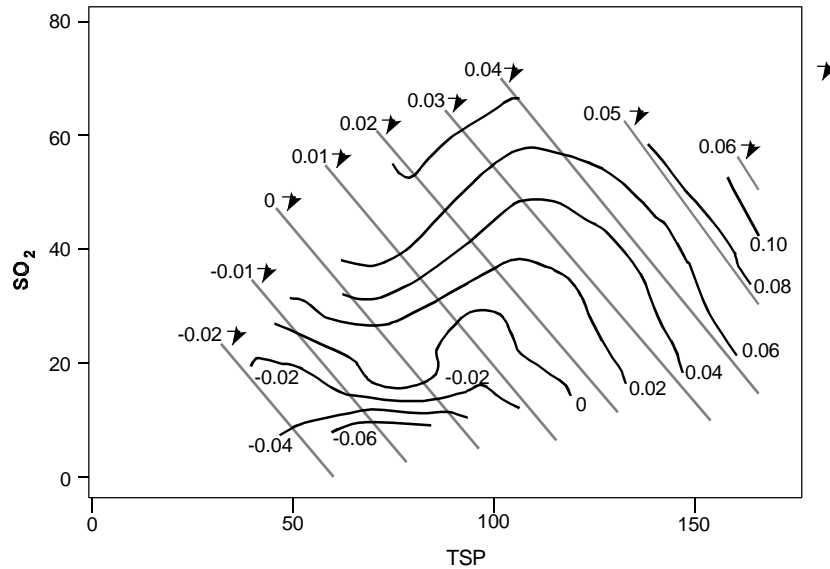
**Figure 12-38. Curved contours depicting the excess risk of total mortality in Philadelphia, by season, for 1983 to 1988.** Straight lines show the excess risk from an additive linear model fitted to the same data, which exhibits significantly inferior goodness of fit relative to the GAM model.

Source: Adapted from Samet et al. (1995).

mortality is changing in relation to the variable on the horizontal axis (TSP), as is suggested for TSP greater than about  $125 \mu\text{g}/\text{m}^3$ . The contours change orientation between  $75$  and  $125 \mu\text{g}/\text{m}^3$  TSP. It is clearly not correct to conclude from the additive linear model that one pollutant is always (or never) a better predictor of excess mortality in Philadelphia than is the other pollutant.

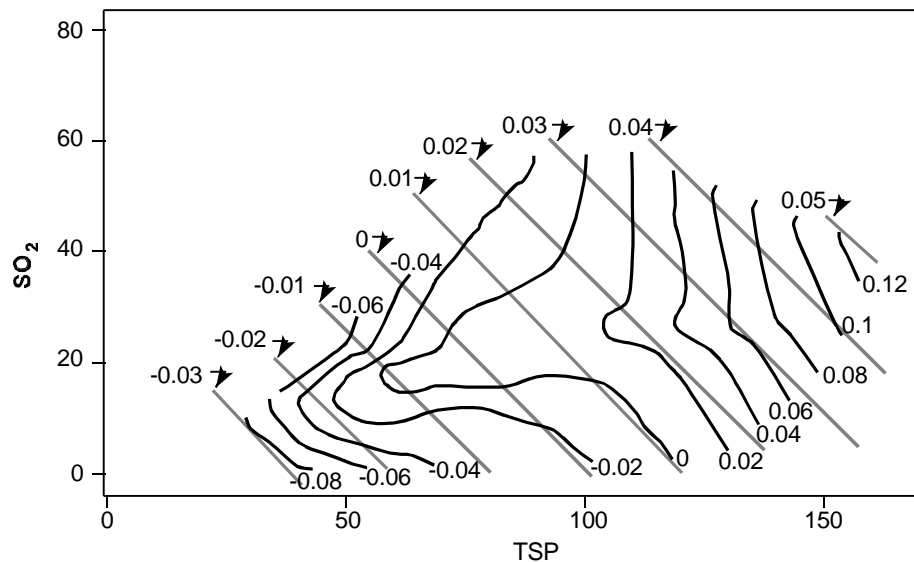
Seasonal differences also seem to play an important role. Figures 12-39 through 12-42 show analogous results from the HEI report for spring, summer, fall, and winter 1973 to 1980 data. In Figure 12-39 (spring), the nonparametric contours for TSP greater than about  $125 \mu\text{g}/\text{m}^3$  are roughly parallel to the straight lines from the additive linear model but spaced irregularly, suggesting an additive but somewhat nonlinear model for TSP and  $\text{SO}_2$  in this range. For TSP below about  $75 \mu\text{g}/\text{m}^3$ , there seems to be little relationship of mortality of TSP.

The summer results are shown in Figure 12-40. For TSP greater than about  $110 \mu\text{g}/\text{m}^3$  and  $\text{SO}_2$  less than about 20 ppb, the nonparametric surface contours are roughly parallel to the additive linear model contours, but more closely spaced. For TSP greater than about



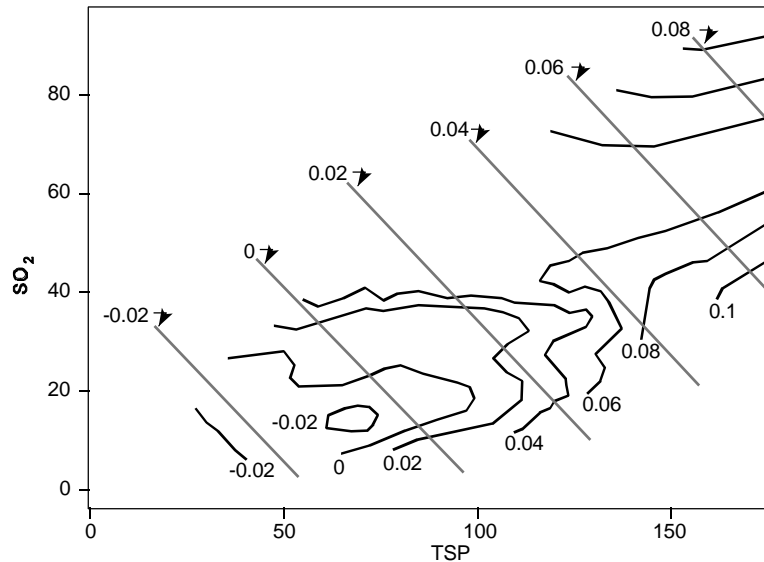
**Figure 12-39.** Contours depicting the fractional change in Philadelphia mortality in spring by levels of total suspended particles (TSP) and sulfur dioxide ( $\text{SO}_2$ ). Straight lines show contours predicted by an additive model. Contours predicted by LOESS with 10.2 equivalent degrees of freedom are shown in the curved lines.

Source: Adapted from Samet et al. (1995).



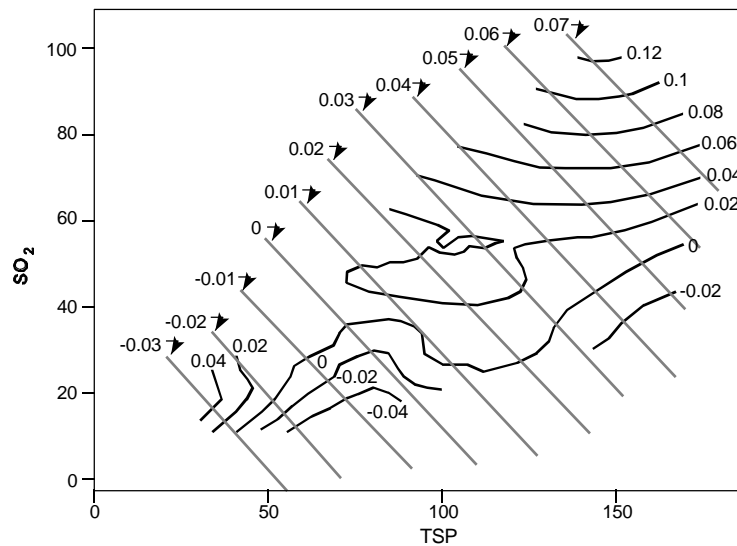
**Figure 12-40.** Contours depicting the fractional change in Philadelphia mortality in summer by levels of total suspended particles (TSP) and sulfur dioxide ( $\text{SO}_2$ ). Straight line show contours predicted by an additive linear model. Contours predicted by LOESS with 10.2 equivalent degrees of freedom are shown in curved lines.

Source: Adapted from Samet et al. (1995).



**Figure 12-41.** Contours depicting the fractional change in Philadelphia mortality in fall by levels of total suspended particles (TSP) and sulfur dioxide ( $\text{SO}_2$ ). Straight lines show contours predicted by an additive linear model. Contours predicted by LOESS with 10.2 equivalent degrees of freedom are shown in curved lines.

Source: Adapted from Samet et al. (1995).



**Figure 12-42.** Contours depicting the fractional change in Philadelphia mortality in winter by levels of total suspended particles (TSP) and sulfur dioxide ( $\text{SO}_2$ ). Straight lines show contours predicted by an additive linear model. Contours predicted by LOESS with 10.2 equivalent degrees of freedom are shown in curved lines.

Source: Adapted from Samet et al. (1995).

110  $\mu\text{g}/\text{m}^3$  and  $\text{SO}_2$  greater than about 20 ppb, the nonparametric surface contours are roughly parallel to the vertical axis, suggesting a fairly strong dependence of mortality on TSP with little additional effect of  $\text{SO}_2$ . For TSP less than 110  $\mu\text{g}/\text{m}^3$ , the contours are very complex and suggest a small excess of mortality for  $\text{SO}_2$  between 20 and 40 ppb, with results for higher values of  $\text{SO}_2$  somewhat uncertain because of the virtual absence of high  $\text{SO}_2$  data on days with low TSP.

Fall results are shown in Figure 12-41. For TSP greater than about 100  $\mu\text{g}/\text{m}^3$  and  $\text{SO}_2$  less than about 40 ppb, the nonparametric surface contours are roughly parallel to the vertical axis, suggesting a strong TSP effect in this range. For TSP less than about 100  $\mu\text{g}/\text{m}^3$ , the nonparametric surface contours are roughly parallel to the horizontal axis, showing little effect of TSP in this range.

Winter results are shown in Figure 12-42. For TSP between about 80 and 100  $\mu\text{g}/\text{m}^3$  and  $\text{SO}_2$  less than about 30 ppb, the nonparametric surface contours are roughly parallel to the vertical axis suggesting some TSP effect, but otherwise  $\text{SO}_2$  appears to be the dominant pollutant for winter mortality since the contour lines generally parallel the horizontal axis. This can be visualized more effectively using the three-dimensional plot in Figure 12-37. One-dimensional nonparametric models for mortality versus TSP and mortality versus  $\text{SO}_2$  are shown in the HEI report (Samet et al., 1995; Figure 11). These figures, based on generalized additive models, suggest a somewhat complex relationship with lower RR for total mortality at TSP less than 90 to 100  $\mu\text{g}/\text{m}^3$ , a sharp increase at higher TSP levels, whereas the relationship of excess mortality to  $\text{SO}_2$  is sharply increasing at  $\text{SO}_2$  below 20 ppb, flat above 20 ppb. The relationship of mortality to TSP is flat for people less than 65 years of age, but sharply increasing at TSP greater than 50  $\mu\text{g}/\text{m}^3$  for people age 65 years or greater. Age and other factors affecting the susceptible subpopulation(s) such as weather and copollutant stresses may be contributing factors in the apparent nonlinear and interaction between PM and other variables that was observed in the multidimensional mortality concentration-response surfaces plotted in Figures 12-36 through 12-42.

While these plots may invite some overinterpretation several important points have been established by the nonparametric modelling of concentration-response surfaces for the Philadelphia mortality data:

- (1) Both TSP and SO<sub>2</sub> were associated with significant increases in mortality in Philadelphia during 1973-1980, even after adjustments for weather-related effects, but there were important differences in effect depending on season and on the range of TSP or SO<sub>2</sub> values;
- (2) There was indication of a relatively large relationship between TSP and excess mortality during spring and summer, for TSP larger than about 100 µg/m<sup>3</sup>; even during these seasons, there was little evidence for a TSP relationship with mortality at substantially smaller TSP concentrations;
- (3) There was a relationship between SO<sub>2</sub> and excess mortality at TSP concentrations below 75 µg/m<sup>3</sup>, but the relationship was not evident at SO<sub>2</sub> concentrations above about 50 ppb or TSP concentrations above about 75 to 100 µg/m<sup>3</sup>;
- (4) There is little basis for assuming that analogous results would be obtained for other PM indices, such as PM<sub>10</sub> or PM<sub>2.5</sub>.

In the studies discussed in Sections 12.3 and 12.4, many of the analyses are based on additive linear models for the copollutants. Based on the preceding discussion, there may be some unresolved questions about the adequacy of the fitted models to accurately characterize the joint effects of the PM index and other pollutants. Therefore the estimated RR and statistical significance of PM and other pollutants as predictors of health endpoints may be biased by the misspecification of the joint or multivariate concentration-response surface for the multiple pollutants.

The excess risk contours change orientation between 75 and 125 µg/m<sup>3</sup> TSP. It is clearly not correct to conclude from the additive linear model results that one pollutant is always (or never) a better predictor of excess mortality in Philadelphia than is the other pollutant. Seasonal differences also seem to play an important role.

The Samet et al. analyses suggest that interpretation of the results of fitting additive linear models using two or more pollutants may be premature without considering in some detail the exact nature of the interactions among the pollutants, and possibly also the effects of interactions (i.e., adjustments and effect modifications) involving weather and other covariates. In particular, the conclusion from an additive linear model that inclusion of copollutants generally lowers the effect attributable to PM may not apply to a more accurate nonparametric model. It is possible that for certain ranges of PM concentrations, inclusion of copollutants in the model makes little or no difference for the estimated PM effect, and for some ranges of the copollutants, the estimated

PM effect might even be larger than the overall PM effect estimated from a linear model. These differences or PM effect modifications may vary from city to city or from season to season. There is little basis for generalizing these findings beyond these 8 years of data from one city.

The underlying problem of modeling multiple pollutants is very similar whether the study data are derived from daily time series, from long-term prospective studies, or from population-based studies. In most analyses of population-based data, an additive linear model for the *logarithm* of the pollutant concentration is used, which may not alter the fundamental problem that the additive linear model may still be a misspecification of the relationship.

The conclusion that the RR estimates from fitting a linear model with a single pollutant are upper bounds of that pollutant's RR should not be taken as true in general, for all pollutants and all concentration ranges. Tests of the adequacy of the additive linear model specification have not been reported in general, and it is likely that investigations of other data sets will find more situations in which the standard additive linear model is not adequate for evaluating the health effects of multiple pollutants.

### ***Summary***

In summary, confounding by weather and by time effects can be adjusted statistically so as to remove a substantial amount of confounding, but possibly at the expense of reducing the estimated PM effect by attributing it to weather or longer-term time effects not related to short-term PM exposure. Confounding by co-pollutants sometimes cannot be avoided, but should be diagnosed and reported more completely than in most studies now available. In studies where sensitivity analyses demonstrate that including other pollutants in the model causes little change in either the RR estimate for PM or on the width of the confidence interval for the PM effect, one may conclude that the model is not seriously confounded by co-pollutants. Since a number of mortality and morbidity studies have shown that the PM effect on health is not sensitive to other pollutants, we may conclude that the PM effects in these studies are real. This adds some credibility to the claim that a significant PM effect exists in the remaining studies where PM is statistically significant in a model without other pollutants, though similar in magnitude to the PM effect found in other studies with less co-pollutant confounding, but is not statistically significant when other pollutants are included in the model. This then provides a basis for the meta-analyses discussed below.

#### **12.6.3.6 Ecological Study Design**

Most of the studies considered are ecologic in design. Even in the daily longitudinal studies, individuals are grouped by region, SMSA, or catchment area for hospital admissions, and all are assumed to have exposure to PM and other covariates characterized by a single numerical value for the area on that day. The "ecological fallacy" refers to the biases inherent in making individual-level predictions from aggregate-level data. However, such studies are often used because of the availability of data bases for air pollution, weather, and mortality or hospital admissions on a daily basis. Relative risk estimates for individuals should therefore be regarded as subject to much uncertainty, even for age-specific sub-populations, in the absence of subject-specific exposure and covariate data. Recent additions to the NCHS mortality data base, including demographic information such as educational attainment, may allow better resolution of the effects of socio-demographic covariates. While residential location might improve estimates of exposure in communities with several monitoring sites, there would still be considerable uncertainty about individual non-residential exposures in the absence of information about daily activity. Better individual exposure information would still be needed to reduce the substantial uncertainties about exposure.

#### **12.6.3.7 Measurement Error**

While there has been much discussion about the effects of measurement error, particularly with respect to exposure misclassification, few suggestions have been made as to how to deal with this question.

There have been few quantitative assessments of errors in measurements of particulate matter or other copollutants. There are at least two major components of these errors.

- (1) Instrument error: Errors in measurement of pollutant levels at the point of measurement.
- (2) Proxy error: Error in using levels at a point (even if correctly measured) as the levels to which study population members are exposed.

For studies of chronic effects, another potentially important problem is sometimes dealt with under the heading of "exposure definition":

- (3) Construct error: Error in using a particular exposure summary other than the biologically relevant exposure (for example, using time-weighted average level when only time above a critical threshold is biologically relevant). This is also encountered in constructing moving averages for short-term studies.

It is often assumed that any measurement error is nondifferential, and that consequently any bias produced by the error would be towards the null. Neither assumption is necessarily correct. There are several possible scenarios under which proxy measurement errors will be differential. For example, suppose monitor readings in low-pollution, low-mortality areas tend to understate exposure more than in high-pollution, high mortality areas because many residents of low-mortality areas commute to jobs in high-mortality areas. Then measurement errors will be differentially higher for low-mortality populations (and among noncases in an individual-level study based on these measurements and areas).

Contrary to popular treatments, nondifferential error does not guarantee that the resulting bias in effect estimates is towards the null. In ecologic designs, nondifferential error in individual-level exposure measurements can easily produce very large bias away from the null. In individual-level designs, nondifferential error may produce bias away from the null if errors are interdependent or if the dependence of measured on true levels is not monotonic. Interdependence of errors seem likely. For example, wind patterns would induce correlated proxy errors in all atmospheric pollutants. Effects of confounder errors can be in either direction, whether or not the errors are nondifferential. Under the best of circumstances the only predictable effect of nondifferential confounder errors is that they will tend to leave the exposure effect estimates partially confounded. A recent study by Schwartz et al. (1996) suggests that the effects may be small in daily mortality studies.

In summary, there has been no evidence presented that measurement errors are nondifferential. Even if there were such evidence, it would not imply that the biases produced by the errors are toward the null. Bias due to measurement error can be profound.

## **12.6.4 Assessment Issues for Epidemiology Studies**

### **12.6.4.1 Significance of Health Effects/Relevancy**

The "relative risks" derived from the regression coefficients in recent short-term PM/mortality studies appear to be consistently "small" (i.e., 1.025 to 1.05 per 50  $\mu\text{g}/\text{m}^3$  increase in  $\text{PM}_{10}$ ), compared (at a face value) to the relative risks in other types of studies. In cancer

epidemiology, for example, some (Shapiro, 1994) consider a relative risk of 1.7 as weak support, "at most", for a causal inference. However, much lower RR estimates of 1.2 to 1.3 have been regarded as sufficient for establishing a presumption of a causal relationship for health effects from environmental pollutants in recent EPA studies on environmental tobacco smoke (U.S. Environmental Protection Agency, 1992) and nitrogen oxides (U.S. Environmental Protection Agency, 1993).

The fact that a relationship is weak, or that an effect is small, does not mean that the relationship is not causal. As Rothman (1986, pp. 17-18) points out, "By 'strength of association', Hill [1965] means the magnitude of the ratio of incidence rates. Hill's argument is essentially that the strong associations are more likely to be causal than weak associations because if they were due to confounding or some other bias, the biasing association would have to be even stronger and would therefore presumably be evident. Weak associations, on the other hand, are more likely to be explained by undetected biases. Nevertheless, the fact that an association is weak does not rule out a causal connection." Many of the studies cited in this chapter included substantial assessments of the effects of potential confounding factors, particularly age group, identifiable cause of death or hospital admission, weather or climate, and the levels of co-pollutants. In some cases, potentially confounding factors were either not present or present at such levels as to have a negligible effect on the health outcome. Even when potential confounders were present, it was often possible to carry out a statistical adjustment for the confounder, with the PM effect size estimated with and without the potential confounder in the model. The PM effect size estimates and their statistical uncertainty in many studies showed little sensitivity to the adjustment for confounding variables. In a few other studies, there was substantial confounding with some co-pollutants such as SO<sub>2</sub> or O<sub>3</sub>, but estimates of RR for PM without inclusion of the confounders in the statistical concentration-effect model used in these studies were quantitatively similar to RR estimates from other studies where confounding was either avoided or was shown statistically to have little effect. This bears out the comment by Rothman (1986, p. 18) that "... the strength of an association is not a biologically consistent feature, but rather a characteristic that depends on the relative prevalence of other causes," which here includes confounders such as weather and co-pollutants.

However, these two types of relative risks are not directly comparable. The "relative risk" estimates used in these short-term PM exposure studies are not only "acute" in their

exposure/response relationship, but also represent "indirect" cause of deaths. A healthy person does not develop respiratory disease and die from an exposure to  $100 \mu\text{g}/\text{m}^3$   $\text{PM}_{10}$  in one day. The causal hypothesis is that people with chronic respiratory or cardiovascular diseases, who may be near death from the preexisting conditions, are pushed toward death prematurely by the additional stress on the respiratory system imposed by an increased level of air pollution. This is in contrast to a cancer risk from exposures to a chemical, through which a perfectly healthy person may develop cancer and die at the age of 50, when the person may otherwise have lived up to 70 years old. This difference may be obvious to the researchers analyzing these data, but needs to be clarified when such "risk estimates" are communicated to people who are not familiar with this field. Estimates of life shortening attributable to short-term and chronic PM exposure are not available.

With this difference taken into consideration, there are several reasons why we may be concerned about the estimated "relative risks":

- The apparent "relative risk" estimates are often calculated for the entire death categories. Cause-specific "relative risk" estimates are often greater than for total mortality (e.g., in Pope et al.'s Utah study, the excess relative risk calculated for the respiratory category mortality was 43% as opposed to 16% for total mortality). If susceptible populations were defined and categorized, for example by age, the risk estimate would be even higher than for the general population.
- The apparent "relative risk" tacitly assumes a baseline death population in which all are subject to the change in PM exposures. It is likely that this is not the case. An unknown fraction of the population are not subject to the change in exposure levels of outdoor PM, thereby causing an underestimation of the risk of those actually exposed.
- There may be a downward bias in the estimated PM/mortality regression coefficients (and, therefore, in the estimated relative risk) due to the PM measurement errors. The extent of this bias is not known.
- The extent of prematurity of the deaths, which may range from days to years, is not known.

#### **12.6.4.2 Biological Mechanisms**

Most of speculation on the biological mechanism of PM mortality effects were made in the earlier major air pollution episodes. According to Firket's report (1936) on the fog episode of Meuse Valley in 1930, the autopsies with microscopical examinations found local and superficial

irritation of the mucus membrane of the respiratory ducts and the inhalation of fine particles of soot in the pulmonary alveoli. The chemists concluded that "the  $\text{SO}_2$  in the presence of oxidation catalysts such as ferric and zinc oxide, must have been partly transformed to sulfuric acid". The discussion of the report suggested sulfuric acid to be "the most probable cause" of deaths. In the 1952 London fog episode (United Kingdom Ministry of Health, 1954), the association of the air pollution and the observed increase in deaths, estimated to be 4,000 excess deaths, was rather obvious. The report suggested "it is probable that sulphur trioxide dissolved as sulphuric acid in fog droplets, appreciably reinforced the harmful effects of sulphur dioxide." One immediate cause of death was speculated to be acute anoxia from bronchospasm.

Health effects observed at current air pollution levels are more subtle, as in recent PM/mortality studies. There are some speculations regarding possible mechanisms, identifying specific chemical components responsible for the effects such as acid aerosols. The pattern that does appear to resemble the past episodes in these more recent observational studies is the age and cause specificity of the deaths associated with PM. Both cardiovascular and respiratory deaths in the elderly population increased in the 1952 London episode. The estimated relative risks for these categories were found to be disproportionately higher and more significant in the analysis of Philadelphia (Schwartz, 1994b,c). Other cause specific analyses (e.g., Fairley, 1990; Pope et al., 1992; Schwartz, 1994b) also reported higher estimated relative risks for respiratory and cardiovascular categories than total or other categories. While the excess deaths in the cardiovascular category, which was also apparent in past episodes, do not provide direct information on possible causal mechanisms, the analysis of contributing causes (Schwartz, 1994h) appears to suggest that the respiratory illness is contributing to the deaths of people with cardiovascular conditions. If a person has been suffering from a major cardiovascular disease, that person's death may be still categorized as cardiovascular, even if the respiratory condition causes the death. Such misclassification may also occur for other categories (e.g., cancer). More analyses using the contributing cause of deaths are needed to further characterize such mechanisms.

#### 12.6.4.3 Coherence

Factors involved in evaluating both the data and the entire group of epidemiological studies, include the strength of association, the consistence of the association, as evidenced by its repeated observation by different persons, in different places, circumstances and time, and the coherence with other known facts (Bates, 1992). One can look for interrelationships between different health indices to provide a stronger and more consistent synthesis of available information. The various findings that support a picture of coherence would provide a stronger case with quantitative studies as opposed to qualitative studies. Other studies may be inappropriate to use in such a discussion, the quality of the study should be considered. Bates (1992) states that the difficulty with discussing any index of internal coherence is that this requires a series of judgements on the reliability of the individual findings and observations. The outcome of a coherence discussion then is a qualitative presentation.

Bates (1992) also noted that the strength of different health indexes are important as are difficulties in assessing exposure. Bates (1992) also suggests three areas to look for coherence: (1) within epidemiological data, (2) between epidemiological and animal toxicological data, and (3) between epidemiological, controlled human and animal data.

Coherence by its nature considers biological relationships of exposure to health outcome. The biologic mechanism underlying an acute pulmonary function test reduction in children is most likely not part of the acute basis for a change in the mortality rate of a population exposed in an older group of individuals. In looking for coherence one can compare outcomes that look at similar time frames—daily hospitalizations compared to daily mortality or acute versus chronic outcomes. Overall the data indicates that PM has a relationship with a continuum of health outcomes, but the underlying mechanisms may be different.

Coherence in the overall data base can be considered within the endpoint and/or in other endpoints. The principal health outcome for which coherence is desirable is mortality, the death rate in a population. Of the various morbidity outcomes studied and discussed in the earlier part of the chapter, hospitalization studies reviewed in the chapter support this notion. The mortality studies suggest that these specific causes provide stronger relationships (i.e., larger RR estimates) than total mortality. The outcome potentially most related is hospital admission for respiratory or cardiovascular causes in the older age group (i.e., > 65 years old). In a qualitative sense, the increased mortality found in that age group are paralleled by increased hospital admissions.

Partial coherence is supported by those studies in which increased incidence of different health outcomes associated with PM are found in elderly populations in different cities, as is the case for the following examples, based on currently published studies:

- Detroit: Mortality mainly in elderly populations, hospital admissions for respiratory causes and for cardiovascular causes in the elderly;
- Birmingham: Mortality mainly in the elderly, hospital admissions for the elderly;
- Philadelphia: Mortality and hospital admissions for pneumonia in the elderly;

In the Utah Valley, several studies have been conducted. Mortality and hospital admissions for respiratory causes in adults have been associated with PM in the Utah Valley. Also, pulmonary function, respiratory symptoms, and medication use in asthmatic subjects of all ages; hospital admissions for respiratory symptoms, pulmonary function, respiratory symptoms, and medication use in healthy school children, pulmonary function in symptomatic and asymptomatic children; and elementary school absences in children were found to be associated with PM exposures in Utah Valley. Another study found a PM effect on pulmonary function in smokers with COPD in Salt Lake Valley. The Utah Valley population was largely non-smoking, so smoking was not likely to be a source of confounding.

While these multiple outcomes did not occur in strictly identical subgroups of each population, there was probably a sufficient degree of overlap to indicate that PM was a significant predictor of a wide range of health outcomes within a specific community. The symptoms serious enough to warrant hospitalization and the major part of the excess mortality occurred in the elderly sub-group of the population. However, a significant decrement in pulmonary function and increased incidence of symptoms associated with daily increases in PM occurred in children in Utah Valley, along with a "quality of life" effect measured by lost school days. Thus, there is evidence for increased risk of health effects related to PM exposure ranging in seriousness from asymptomatic pulmonary function decrements, to respiratory symptoms and cardiopulmonary symptoms sufficiently serious to warrant hospitalization, and to excess mortality from respiratory and cardiovascular causes, especially in those older than 65 years of age.

Children may also be at increased risk of pulmonary function changes and increased incidence of symptoms associated with PM exposure. While we have arrayed these health outcomes in order of increasing severity, there is as yet little indication that there is a progression

of effects in any single individual associated with increasing exposure to PM. The "exposure-response" relationship that is derived in most studies must be understood as characterizing population risk from population exposure. Additional studies are needed to define the relationship(s) among individual exposure to PM and other stress factors, individual risk, and individual progression among disease states. Differences in PM dosimetry in the developing, aged, or diseased respiratory tract may also contribute to increased susceptibility.

## **12.6.5 Meta-Analyses and Other Methods for Synthesis of Studies**

### **12.6.5.1 Background**

Several reports have appeared in which results from different studies have been combined, formally or informally, to present an overall effect size estimate for acute health effects. For example, a synthesis of daily mortality studies for seven cities was published by Schwartz (1992a). The seven cities included four TSP studies (Steubenville, Philadelphia, Detroit, Minneapolis) and three PM<sub>10</sub> studies (St. Louis, Eastern Tennessee, Utah Valley). The daily mortality studies were further analyzed by Schwartz in a later paper (1994b), which added studies from New York, from Birmingham, Alabama, later London studies (1959 to 1972), and a study in Athens, Greece. The RR estimates were combined in formal quantitative meta-analyses, using either unweighted RR estimates, or using a smaller set of estimates weighted by inverse of the estimation variance of the RR coefficient from studies in which the standard error was reported. Several methods were used, and several subsets of the data were tested according as to whether or not the study city was "warm" or the TSP coefficient was adjusted for copollutants.

A recent paper by Dockery and Pope (1994b) extends the research synthesis to a variety of health outcomes, including hospital admissions studies and respiratory function tests. This paper is also based on conversion of different PM measures to an equivalent PM<sub>10</sub> by applying a scaling factor: 1.0 for PM<sub>15</sub> and BS, 0.55 for TSP, 4 for sulfates (SO<sub>4</sub>), 1/0.60 for PM<sub>2.5</sub>, and 1/0.55 for COH. This synthesis paper uses eight cities for total mortality, four cities for respiratory mortality and for cardiovascular mortality, three cities for hospital admissions for respiratory symptoms, four studies for asthma admissions, and combines three cities with different reasons for emergency room visits. The paper examines the effects of PM on exacerbation of asthma by combining results of two cities for bronchodilator use, and combining three studies for asthmatic attacks. Pulmonary function tests are synthesized from four studies for Forced Expired Volume (FEV<sub>1</sub> and

FEV<sub>0.75</sub>), and six studies for Peak Expiratory Flow (PEF daily, weekly, or longer). Respiratory symptom results are divided into combining six studies reporting lower respiratory symptom results, upper respiratory symptom results, and six studies reporting cough symptom results. The authors conclude that these results demonstrate a coherence of effects across a range of related health outcomes, and a consistency of effects across independent studies by different investigators in different settings.

The synthesis of the epidemiologic evidence in this document presents some unusual problems. Many of the studies showing mortality and morbidity effects are based on relatively small increases estimated with great precision resulting from sophisticated analyses of long series of infrequent events. As a result, relative risks (or odds ratios) of 1.06 are common and often statistically significant. A value of 1.06 would indicate that mortality (or morbidity) is increased by 6% when PM<sub>10</sub> is increased a specified amount (usually 50  $\mu\text{g}/\text{m}^3$ ). Traditionally, relative risks less than 1.5 were considered to be of questionable biological meaning. Although relative risks near 1.06 are not large in magnitude, they may represent a large net effect because the events are so common. The question remains: are these effects real or are they an artifact of the analysis?

A careful review of the analysis techniques in Section 12.6.3 suggests that similar results are obtained as long as similar covariates and independent variables are included in the analysis. There are remaining questions about the accuracy of the variances and the assumptions upon which they are based. Even allowing for these problems, the estimated regression coefficients are consistently estimating the correct quantities although the exact p-values may be slightly in error.

The results do not appear to depend heavily on the form in which covariates were included in the model. Analyses that included the known covariates such as temperature and season usually gave similar results. The one factor which appeared to make a consistent difference was the inclusion of one or more copollutant(s) in addition to particulate matter. The inclusion of SO<sub>2</sub> tend to reduce the effect of particulate matter in most analyses, while O<sub>3</sub> generally had less of an impact on PM regression coefficients. This would be expected because O<sub>3</sub> tends to be less correlated with PM than does SO<sub>2</sub>. Although the PM coefficients were reduced by the inclusion of SO<sub>2</sub>, most remained statistically significant.

One unresolved question is the possibility that the effects seen were the result of some covariate which, had it been included, would have reduced the PM coefficients to a non-significant level. Although this is always a concern with epidemiologic studies, the concern is

often dismissed as improbable when the relative risks are large as 1.5 or 2.0. When the relative risks are less than 1.1, the question is of greater concern.

#### **12.6.5.2 Meta-Analyses Using Studies Reviewed in This Document**

In order to compare the results of the various studies relating acute exposure to PM to excess mortality, we selected studies that satisfied certain criteria: (1) the study has been published or is in press; (2) the study used PM<sub>10</sub> or TSP as an index of particulate matter exposure; and (3) the study included adequate adjustments for seasonality, weather, other effects. The first criterion was imposed to provide adequate access to a description of study data, methods, and results; and the second so as to restrict consideration to studies with pollutants for which EPA has extensive air monitoring data. Even here, analyses were performed separately for PM<sub>10</sub> studies and for TSP studies, so as to avoid having to make any assumptions about site-specific calibrations of one PM concentration or index into another. It may be possible to extend the meta-analyses to a wider range of studies when methods are developed for assessing the uncertainty associated with generic versus city-specific calibrations of one PM index to another.

The results of the analyses have been standardized for purposes of comparison. All of the acute exposure studies used Poisson or equivalent regression methods with the expected mortality an exponential function of a linear combination of predictors, or with the logarithm of the mortality rate as a linear combination of predictors including the PM index. This means that the relative risk (RR) -- the fractional increase in the mortality rate relative to a baseline value without pollution, everything else being equal -- can be expressed in terms of changes per unit of pollution. The base unit for change in risk was chosen differently for each pollutant. For PM<sub>10</sub> studies, the effect was the odds ratio for mortality corresponding to an increase of 50  $\mu\text{g}/\text{m}^3$  in PM<sub>10</sub>. Other ranges have been used in published papers, most commonly 10 or 100  $\mu\text{g}/\text{m}^3$ . We selected 50  $\mu\text{g}/\text{m}^3$  because it is closer to the range of values in various morbidity studies, whereas the range in mortality studies usually is larger than 100  $\mu\text{g}/\text{m}^3$ . Since the range of values in TSP studies is typically much larger than in PM<sub>10</sub> studies, we used 100  $\mu\text{g}/\text{m}^3$  as the base unit for TSP studies of mortality.

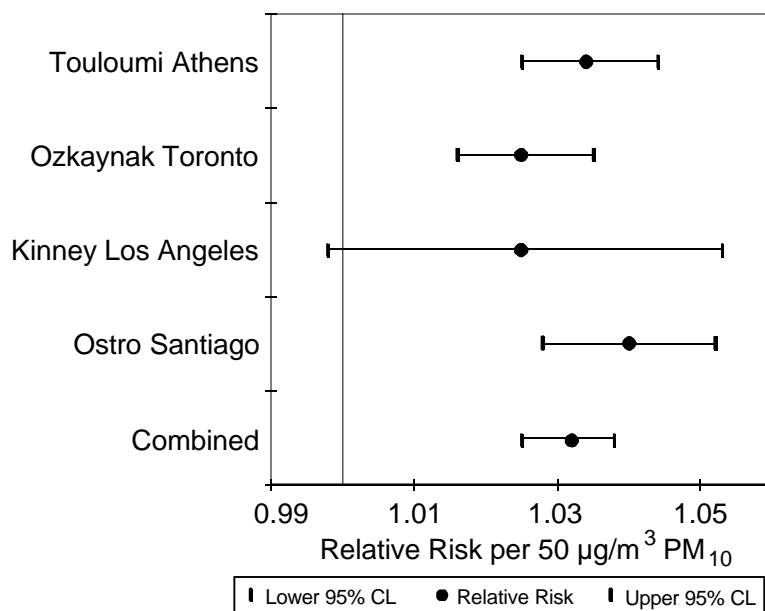
The basic data on effects size estimates, in appropriate units, are shown earlier in Tables 12-2 and 12-4. Note that the confidence intervals derived in the various papers are not

always symmetric about the estimated RR. The data could be naturally sorted into six distinct groups:

- Estimates of PM<sub>10</sub> effect on RR, not adjusted for copollutants, lags <2 d (4 studies, 4 cities)
- Estimates of PM<sub>10</sub> effect on RR, not adjusted for copollutants, lags >2 d (6 studies, 6 cities)
- Estimates of TSP effect on RR, not adjusted for copollutants (4 studies, 3 cities)
- Estimates of PM<sub>10</sub> effect on RR, adjusted for copollutants (3 studies, 3 cities)
- Estimates of TSP effect on RR, adjusted for SO<sub>2</sub> (3 studies, 2 cities)
- Estimates of PM<sub>10</sub> effects on RR short, long lags (3 studies, 3 cities)

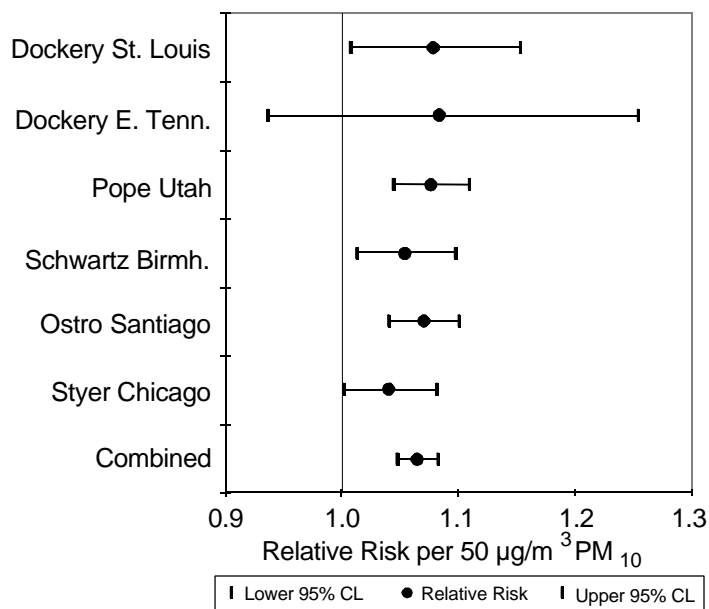
There are presently no methods for using results of different analyses of the same data set, such as the two studies on Steubenville (Schwartz and Dockery, 1992b; Moolgavkar et al., 1995a). (For this assessment, we report results using each separately.)

The meta-analysis methods were similar to those used in the nitrogen oxides criteria document (U.S. Environmental Protection Agency, 1993; Hasselblad et al., 1992). Differences among studies are regarded as random effects. The U.S. EPA meta-analyses results are shown in Figures 12-43 through 12-48 and Table 12-33. The relative risk for



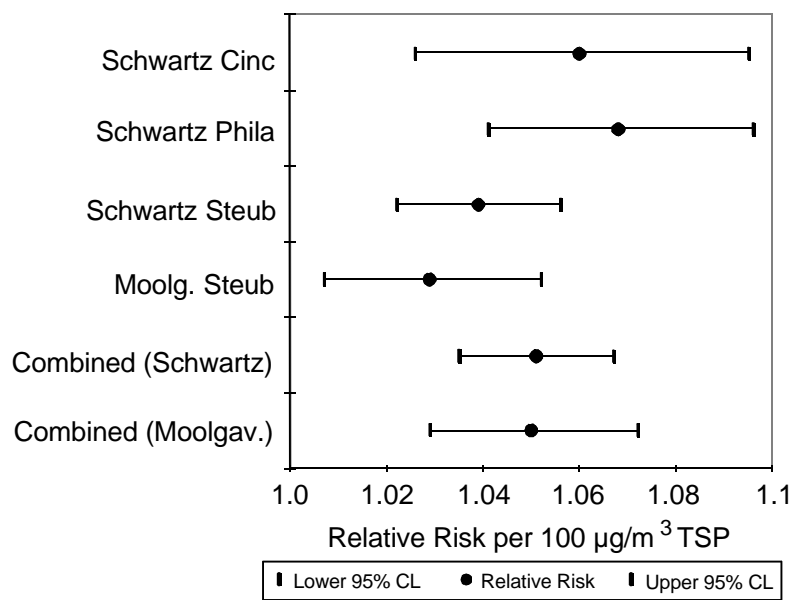
**Figure 12-43. Summary of studies used in a combined U.S. Environmental Protection Agency meta-analysis of PM<sub>10</sub> effect on mortality with short averaging times (0 to 1 day), and co-pollutants in the model.**

Source: Touloumi et al. (1994); Ozkaynak et al. (1994); Kinney et al. (1995), and Ostro et al. (1996).



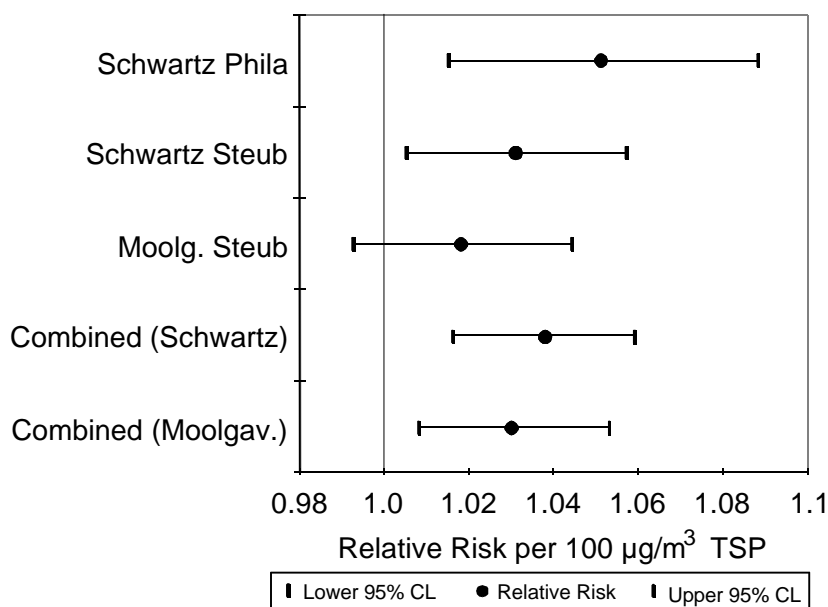
**Figure 12-44. Summary of studies used in a combined U.S. Environmental Protection Agency meta-analysis of PM<sub>10</sub> effects on mortality with longer averaging times (3 to 5 days), and no co-pollutants in the model.**

Source: Dockery et al. (1992); Pope et al. (1992); Schwartz et al. (1993a); Ostro et al. (1995b); and Styer et al. (1995).



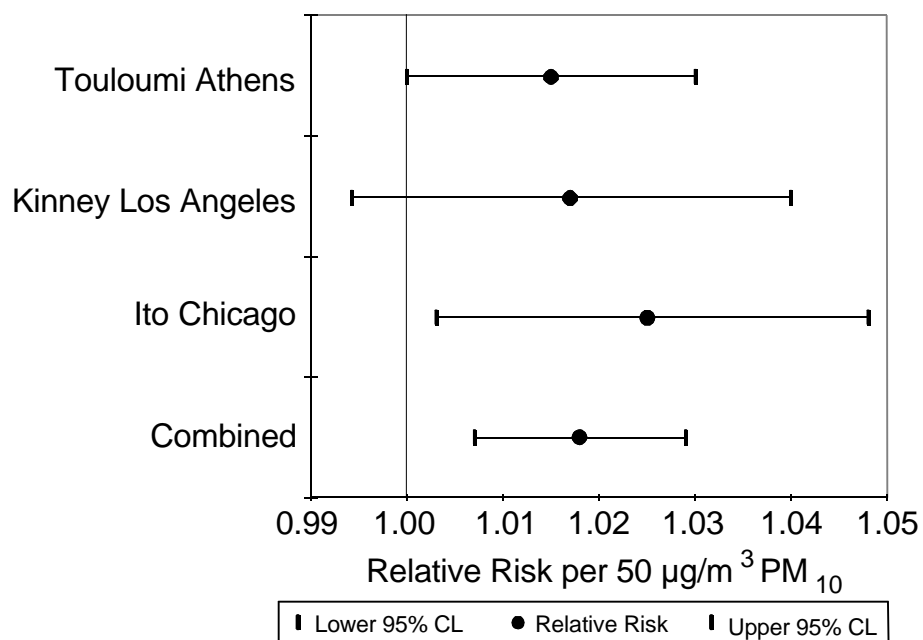
**Figure 12-45. Summary of studies used in a combined U.S. Environmental Protection Agency meta-analysis of total suspended particles (TSP) effects on mortality, with no co-pollutants in the model.**

Source: Schwartz (1994a); Schwartz and Dockery (1992a); Schwartz and Dockery (1992b); Moolgavkar et al. (1995a).



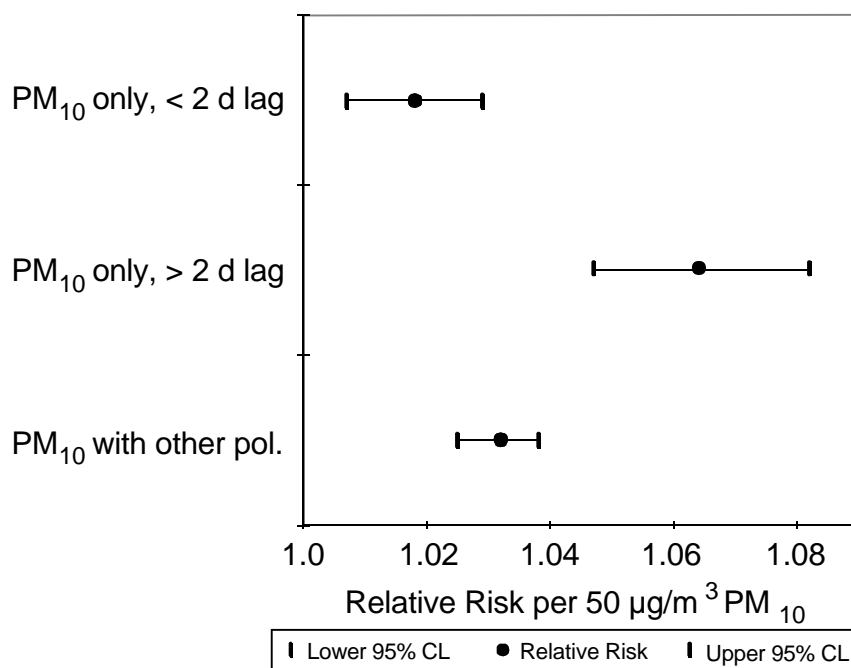
**Figure 12-46. Summary of studies used in combined U.S. Environmental Protection Agency meta-analysis of total suspended particles (TSP) effects on mortality, with sulfur dioxide in the model.**

Source: Schwartz and Dockery (1992a); Schwartz and Dockery (1992b); Moolgarvkar et al. (1995a).



**Figure 12-47. Summary of studies used in a combined EPA meta-analysis of PM<sub>10</sub> effects on mortality, with other pollutants in the model.**

Source: Touloumi et al. (1994); Kinney et al. (1995); Ito et al. (1995).



**Figure 12-48. Summary of PM<sub>10</sub> effects on mortality.**

Source: U.S. Environmental Protection Agency meta-analyses.

PM<sub>10</sub> exposure averaged ≤2 days is estimated as 1.031 per 50 µg/m<sup>3</sup> PM<sub>10</sub>, with a 95% confidence interval of 1.025 to 1.038 per 50 µg/m<sup>3</sup> PM<sub>10</sub>. There is overall evidence of an effect, even though one of the four studies in Figure 12-43 is not significant. The relative risk for PM<sub>10</sub> exposure with longer averaging times, 3 to 5 d, is estimated as 1.064 with 95% confidence interval of 1.047 to 1.082. In Figure 12-44, one study is negative and another marginally significant. The combined estimate for TSP effect in Figure 12-45 depends on which study is used for the Steubenville estimate; with the Schwartz study, the effect is 1.051 per 100 µg/m<sup>3</sup> TSP, whereas with the Moolgavkar study, the estimate is 1.050, but is less certain. However, none of these studies included SO<sub>2</sub>, the most probable confounding co-pollutant. The analogous estimates for a TSP effect with copollutants in the model is less significant across three studies, as shown in Figure 12-46. Also, Figure 12-47 shows that when SO<sub>2</sub> is included in the model, estimated PM<sub>10</sub> effects still remain significant. RR = 1.018 with a 95% confidence interval from 1.007 to 1.029 per 50 µg/m<sup>3</sup> PM<sub>10</sub>. The overall EPA meta-analyses results are summarized in Table 12-37 and Figure 12-48.

**TABLE 12-37. U.S. EPA META-ANALYSES: COMBINED ESTIMATES OF RELATIVE RISK OF INCREASED MORTALITY FROM ACUTE EXPOSURE TO AIR POLLUTANTS**

Pollutant	Increment	Model	Averaging Time	Relative Risk Estimate Per Increment	95 Percent Confidence Limits
PM <sub>10</sub>	50 µg/m <sup>3</sup>	No copollutant	0-1 days	1.031	1.025 to 1.038
PM <sub>10</sub>	50 µg/m <sup>3</sup>	No copollutant	3-5 days	1.064	1.047 to 1.082
TSP	100 µg/m <sup>3</sup>	No SO <sub>2</sub>		1.051 <sup>1</sup>	1.035 to 1.067
TSP	100 µg/m <sup>3</sup>	No SO <sub>2</sub>		1.050 <sup>2</sup>	1.029 to 1.072
PM <sub>10</sub>	50 µg/m <sup>3</sup>	+copollutants		1.018	1.007 to 1.029
TSP	100 µg/m <sup>3</sup>	+SO <sub>2</sub>		1.038	1.016 to 1.059
TSP	100 µg/m <sup>3</sup>	+SO <sub>2</sub>		1.030	1.008 to 1.053

<sup>1</sup>Including Schwartz Steubenville study.

<sup>2</sup>Including Moolgavkar Steubenville study.

We conclude that there is a short-term increase in mortality in response to acute PM exposures. This appears to be at least partly confounded with other pollutants, especially SO<sub>2</sub>,

but even with SO<sub>2</sub> included in the model the effect is on the order of 1 to 5% increase in relative risk per 100 µg/m<sup>3</sup> TSP. This is probably a minimum estimate of effect size. If SO<sub>2</sub> is in fact a proxy for fine particle exposure through the SO<sub>2</sub> to sulfate to fine particle pathway, then adjusting for SO<sub>2</sub> may overcontrol the estimate of PM effect, which could be as large as 1 to 5% per 100 µg/m<sup>3</sup> TSP, or 2 to 6% per 50 µg/m<sup>3</sup> PM<sub>10</sub>. This also depends on PM<sub>10</sub> averaging times, with a 3% increase for averages of current and preceding day PM<sub>10</sub> and 6% effect for 3 to 5 day moving averages.

These analyses suggest that there is an identifiable effect of PM exposure on increases in acute mortality, even when characterized by TSP, a relatively insensitive index of thoracic particle concentration. The role of SO<sub>2</sub> as a possible proxy for fine particle exposure remains to be clarified. It is also not possible to overlook the potential confounding effects of other pollutants such as O<sub>3</sub> and NO<sub>2</sub>.

#### **12.6.5.3 Synthesis of Prospective Cohort Mortality Studies**

The results of the prospective cohort mortality studies are shown in Table 12-16. The California nonsmoker study is not readily compared quantitatively to the other two studies and so will not be used in a quantitative synthesis. The ACS and Six City studies have many points of similarity, as demonstrated in Table 12-38. Two kinds of relative risk comparison are shown for all causes of death, for death by lung cancer and by cardiopulmonary causes, and for all other internal and external causes. The first comparison between the ACS and Six City studies is the relative risk of smoking for current smokers compared to never-smokers. Even though these two studies were completely independent, covering different populations with different recruitment strategies, the general and disease-specific risk rates of smoking for the two studies are strikingly similar, suggesting that other results from the studies may be sensibly compared or combined. The last three columns in Table 12-38 compare the risk rates of the least polluted and most polluted cities in the respective studies. There are two comparisons for the ACS study, based on 151 cities with sulfate data and 50 cities with fine particle data, and 6 cities in the other study. Steubenville OH was the most polluted comparison city in the ACS sulfate and Six City comparison, and the community of

**TABLE 12-38. ADJUSTED MORTALITY RISK RATIOS FOR SMOKING AND FOR PARTICULATE MATTER EXPOSURE BY CAUSES OF DEATH IN TWO RECENT PROSPECTIVE COHORT STUDIES**

Cause of Death	Current Smokers Versus Non-smokers		Most Versus Least Polluted City <sup>1</sup>		
			ACS		6-City
	ACS	6-City	Sulfate	PM <sub>2.5</sub>	----
All Causes	2.07 (1.75, 2.43)	2.00 (1.51, 2.65)	1.15 (1.09, 1.22)	1.17 (1.09, 1.26)	1.26 (1.08, 1.47)
Lung Cancer	9.73 (5.96, 15.9)	8.00 (2.97, 21.6)	1.36 (1.11, 1.66)	1.03 (0.50, 1.33)	1.37 (0.81, 2.31)
Cardio-pulmonary	2.28 (1.79, 2.91)	2.30 (1.56, 3.41)	1.26 (1.16, 1.37)	1.31 (1.17, 1.46)	1.37 (1.11, 1.68)
All other	1.54 (1.19, 1.99)	1.46 (0.89, 2.39)	1.01 (0.92, 1.11)	1.07 (0.92, 1.24)	1.01 (0.79, 1.30)

<sup>1</sup>ACS sulfates, 151 cities (Great Falls, MT versus Steubenville, OH); ACS fine particles, 50 cities, (Albuquerque, NM versus Huntington, WV); Six City study (Portage, WI versus Steubenville, OH).

Huntington, WV (also in Ohio River valley) the most polluted community in the fine particle comparison. The RR for 25  $\mu\text{g}/\text{m}^3$  PM<sub>2.5</sub> is 1.17 (1.09, to 1.26) in the ACS study and 1.31 (1.11 to 1.68) in the Six-City Study. The RR for 15  $\mu\text{g}/\text{m}^3$  sulfate is 1.10 (1.06 to 1.16) in the ACS study and 1.46 (1.16 to 2.16) in the Six City Study. The average for the two studies (random effects weighting) is RR = 1.18 (1.04, 1.33) for 25  $\mu\text{g}/\text{m}^3$  PM<sub>2.5</sub> and RR = 1.11 (0.90 to 1.36) for 15  $\mu\text{g}/\text{m}^3$  sulfate.

#### 12.6.5.4 Discussion

In general, there appears to be a range of acute health responses to air pollution exposure as characterized by some PM indicator. Dockery and Pope (1994b) have stated that "It is ... presumptuous to assign these adverse health effects solely to the mass concentration of particulates. ... Many health effects of particles are thought to reflect the combined action of the diverse components of the pollutant mix." Since pollutant mixes and exposed populations differ from one location to another, it is more probable that there are real differences among different studies.

Several approaches to estimating a combined PM effect as a weighted average of study-specific effects may be considered: (1) regard each effect size estimate as a measurement in an ecological study and adjust for differences in effect size among cities as a function of differences in climate, mixture of other air pollutants, and differences in demographic characteristics; (2) carry out multiple comparisons of effect size estimates and group together those estimates that are not significantly different; (3) perform combined analyses in which the PM effect size parameter(s) are constrained to be equal in different data sets.

With the first approach (1), it may be possible to model the differences in PM effect size estimates by multiple regression on known quantitative differences in climate, copollutant mix, and population. This would require a "meta-regression" in which some assumptions would need to be made about the relationship between PM effect size and the inter-study variables that distinguish different cities, adding yet another layer of uncertainty about model specification. It would not be feasible to carry out this analysis unless there were a large enough number of studies, since multiple linear regression models do not perform well unless there are several times as many data values (effect size estimates from different studies) as there are variables that are used for adjustment.

With approach (2), each effect size estimate for which there was an attached standard error estimate would be compared with each other effect size estimate, as if each effect size estimate was a separate group mean in an analysis of variance. The effect size estimates would then be grouped into clusters in which the cluster members (studies) were not statistically different from each other, although some methods allow for the possibility of partially overlapping clusters. A variety of multiple comparison procedures are available, using either methods based on normally distributed data or more robust methods (e.g., Hochberg and Tamhane, 1987). Some comparisons of a multiple hypothesis testing approach with a metaanalysis approach are described by Westfall and Young (1993), who prefer computer-intensive resampling methods such as bootstrap estimation or permutation testing that may not be feasible unless raw data were available. Conventional multiple testing methods can be done without raw data when standard error estimates are available, and may be especially suitable when there are only a few effect size estimates.

With alternative approach (3), it is essential that raw data be available. It is unlikely that raw data for all studies of any specified health outcome could be assembled within a short period of time, and even then it would likely take months to conduct such an analysis adequately.

The formal meta-analytic methods used to combine effect size estimates for acute mortality (Schwartz, 1994c) or for a variety of health outcomes (Dockery and Pope, 1994b) could possibly be improved by including more information when weighing the studies, as suggested above. There are still many unresolved questions about how the synthesis of PM health effects data from different studies should be carried out.

## **12.7 SUMMARY AND CONCLUSIONS**

Several uncertainties need to be considered in interpreting the PM epidemiology studies individually and as a group. Measurement error in exposure is potentially one of the most important methodological problems, and potential confounding due to weather, copollutants and other factors also needs to be considered. Important potential covariates should be adequately controlled, and the response variable should vary as a function of increasing PM exposure. In addition, quantitative studies must estimate PM exposure with reasonable accuracy as a continuous variable. While individual PM studies may not fully take into account the above uncertainties and considerations, as a group, especially within one study type (i.e., acute mortality), PM studies present a relatively consistent picture. Their use in establishing concentration-response parameters, however, still argues for caution in interpreting these studies because no biological mechanism is known for the increases in mortality related to low level ambient PM exposure.

### **12.7.1 Mortality Effects of Particulate Matter Exposure**

The time-series mortality studies reviewed in this and past PM criteria documents provide strong evidence that ambient air pollution is associated with increases in daily human mortality. Recent studies provide confirmation that such effects occur at routine ambient levels, extending to 24 h concentrations below  $150 \mu\text{g}/\text{m}^3$  (the level of the present U.S. air quality standards). Furthermore, these new PM studies are consistent with the hypothesis that PM is the air pollutant

class most closely associated with the mortality impacts of air pollution. One of the more important findings is that longer averaging times (3 to 5 day moving averages) predict larger and more significant effects on total, respiratory, or cardiovascular mortality in many studies than do PM concentrations on the same or preceding day. Overall as noted in Table 12-4, the PM<sub>10</sub> relative risk estimates derived from the recent PM<sub>10</sub> total mortality studies suggest a 24-h average 50  $\mu\text{g}/\text{m}^3$  PM<sub>10</sub> increase in acute exposure has an effect on the order of  $\text{RR} = 1.025$  to 1.05 in the general population. Higher relative risks are indicated for the elderly and for those with pre-existing respiratory conditions, both of which represent sub-populations at special risk for mortality implications of acute exposures to air pollution, including PM. Results are very similar over a range of specifications of statistical models used in the analyses, and are not artifacts of the methods by which the data were analyzed.

A growing body of evidence suggests that fine particles (PM<sub>2.5</sub>) are most strongly related to excess mortality in both acute and chronic studies. However, while coarse inhalable particles are less strongly implicated in excess mortality, there appears to be some situations in which they may also be predictive of excess mortality.

Evidence for or against threshold effects or other nonlinearities in response is as of yet equivocal. Statistical significance tests for piecewise linear models with a range of cut points (possible thresholds) for effects of TSP on mortality in Philadelphia (Cifuentes and Lave, 1996) show some indication of a nonlinear relationship, with a generally flatter linear relationship between mortality and TSP below the cutpoint than above the cutpoint. However, both linear segments have statistically significant positive regression coefficients at cutpoints around 90  $\mu\text{g}/\text{m}^3$  TSP, even when other pollutants (SO<sub>2</sub>, O<sub>3</sub>) are included in the model and the TSP regression coefficients do not appear to be significantly different between the two segments, suggesting that there may not be a threshold for effect. Other analyses of Philadelphia daily mortality series (Samet et al., 1995) suggest that the relationship is moderately nonlinear and nonadditive, but do not provide evidence for either a TSP threshold or a SO<sub>2</sub> threshold. There is strong evidence that the relationships vary by season, however. The Philadelphia results may reflect seasonal or daily changes in the composition and size distribution of TSP. Other acute studies suggest that the relationship between mortality or hospital admissions and PM<sub>10</sub> do not differ significantly from a linear relationship. On the other hand, some long-term mortality studies suggest a possible threshold for TSP or sulfates. However, because of possible exposure

measurement errors and limited numbers of quantile observations available in piecewise analyses, the detection of a threshold or strongly nonlinear concentration-response relationships may be essentially impossible even if such a relationship actually exists.

There is an indication among these various analyses that children may be more susceptible to the mortality effects of air pollution exposure than the population in general, but it is difficult, given the limited and somewhat conflicting results available at this time, to ascribe any such association to PM pollution in particular. This is an area where further research is clearly needed to broaden the base upon which to assess the potential for PM to increase mortality among children.

Long-term exposure to air pollution was studied by use of cross-sectional studies, comparing rates of mortality or morbidity at a point in time against differences in annual average pollutant concentrations. Most older mortality studies were population-based cross-section studies. These studies used outcome rates for entire cities or SMSA's. Several recent prospective cohort-based cross-sectional studies allow use of subject-specific information about other health risk factors, such as cigarette smoking or occupational exposure; and subject-specific outcome measures. The relative risk estimates show some sensitivity to model specification. For models of 1980 mortality from all natural causes, the RR from separate OLS regression models using TSP,  $PM_{15}$ ,  $PM_{2.5}$  or  $SO_4$  as PM indicators all showed a positive but statistically, non-significant effect. The  $PM_{15}$  RR is 1.036 at  $PM_{15} = 50 \mu g/m^3$  (95% confidence interval 0.98 to 1.10), whereas a log-linear model for the same 62 SMSA's found a larger and statistically significant RR for TSP of 1.066 (95% confidence interval 1.006 to 1.13 at  $TSP = 100 \mu g/m^3$ ). The relative risk of major cardiovascular disease (CVD) for sulfate particles was 1.19 at  $SO_4 = 15 \mu g/m^3$  (interval 1.03 to 1.35) when adjusted for one set of demographic covariates, but smaller and not significant after adjustment with a larger set of covariates. The relative risk of COPD for TSP at  $TSP = 100 \mu g/m^3$  or for non-sulfur TSP was highly significant, 1.50 and 1.43 with confidence intervals (1.22, 1.83) and (1.20, 1.71), respectively.

Although most of these studies covered the entire U.S. using the basic paradigm of Lave and Seskin (1970), there are major differences in the numbers of independent variables considered, including the air pollutants. Most of the studies found pollutant elasticities (i.e., mean effects) of 0.02 to 0.08, although the specific pollutants associated with mortality varied. However, all of these studies found at least some association between air pollution and mortality

on an annual average basis. There was a slight suggestion that elasticities may be decreasing over time (1960 to 1980). It was not possible to determine whether the mortality associations were stronger for pollution measured the same year or in previous years. Analyses by age and cause of death were limited; the most consistent associations found by Lipfert (1994a) were for the elderly, especially ages 75+, and for respiratory disease mortality and TSP.

Two older and three newer prospective cohort studies of mortality associated with chronic PM exposures were also evaluated. Table 12-16 summarizes the three newer prospective studies considered. The two early studies not shown in Table 12-16 were largely inconclusive, and the studies of California nonsmokers by Abbey et al. (1991a, 1995a,b,c) found no significant mortality effects of previous air pollution exposure. That study, however, and the Six-City chronic mortality study, suffer from small sample sizes and inadequate degrees of freedom, which partially offset the specificity gained by considering individuals instead of population groups. The Six Cities and ACS studies agree in their findings of strong associations between fine particles and excess mortality, but it is unfortunate that the ACS study did not consider a wider range of pollutants so as to also evaluate the extent to which other air pollutants may have contributed to the reported PM effects.

The RR estimates for total mortality are large and highly significant in the Six-Cities study. With their 95 percent confidence intervals, the RR for  $50 \mu\text{g}/\text{m}^3$   $\text{PM}_{15}$  is 1.42 (1.16, 2.01), the RR for  $25 \mu\text{g}/\text{m}^3$   $\text{PM}_{2.5}$  is 1.31 (1.11, 1.68), and the RR for  $15 \mu\text{g}/\text{m}^3$   $\text{SO}_4$  is 1.46 (1.16, 2.16). The estimates for total mortality in the ACS study are much smaller, but also much more precise, 1.17 for  $25 \mu\text{g}/\text{m}^3$   $\text{PM}_{2.5}$  (RR 1.09, 1.26), and 1.10 for  $15 \mu\text{g}/\text{m}^3$   $\text{SO}_4$  (RR 1.06, 1.16). Both studies used Cox regression models and were adjusted for rather similar sets of individual covariates. In each case, however, caution must be applied in use of the stated quantitative risk estimates, given that the life-long cumulative exposures of the study cohorts (especially in the dirtiest cities) included distinctly higher past PM exposures than those indexed by the more current PM measurements used to estimate the chronic PM exposures of the study cohorts. Thus, lower risk estimates than the published ones are apt to apply.

An additional line of evidence concerning long-term effects may be seen in comparing some specific causes of death in the prospective cohort studies. Table 12-38 shows relative risk for total mortality, lung cancer deaths, cardiopulmonary deaths, and other deaths in the Six City Study and the ACS study. The RR for current smokers in these two independent studies is very

similar, with no significant differences. The RR for most and least polluted cities in the two studies is the same for total, cardiopulmonary, and other causes of mortality, and the same for lung cancer for sulfates in the ACS study and the Six City study, but not for  $PM_{2.5}$  in the ACS study. It is interesting that Abbey et al. (1991a) found a statistically significant relationship between female cancer and TSP in the AHSMOG study, although not for heart attacks or non-external mortality.

Cross-sectional studies may find a significant association between mortality and a specific air pollutant for any of several reasons:

- The association may reflect a non-zero integral of the acute effects of that pollutant over the period of study.
- The association may reflect a chronic effect from long-term exposures.
- The association may have resulted from confounding, either with another pollutant, with the characteristics of the sources that produced that pollutant (occupational hazards or exposures), or with human elements spatially associated with pollution sources such as differential migration of the healthy, less desirable housing near sources, or other socioeconomic factors.

The studies reviewed above probably all reflect some varying combinations of these possibilities.

Some of the prospective studies demonstrated that including additional pollutant exposures in a statistical model (smoking, occupational exposure) not reflected in the outdoor measurements leads to a stronger statistical mortality relationship with the outdoor measurements. This suggests two possibilities (there may be others):

- The indoor and outdoor exposures may reinforce each other and thus may have similar physiological effects. This may provide some clues as to the most likely of several collinear outdoor pollutants. The responses could be either chronic or acute.
- The indoor or occupational exposures may have created a disease state (independent of the outdoor exposures) that makes the individual more susceptible to outdoor pollution effects.

Distinguishing between these two scenarios will likely require additional research, probably including temporal studies of long-term changes in air quality in different places.

At this time, the results of the long-term studies provide support for the existence of short-term increases in mortality which are not subsequently canceled by decreases below normal rates, as well as for the existence of chronic effects above and beyond the acute PM exposures. Also,

they provide no convincing evidence as to the specific pollutant(s) involved, and they do not rule out the existence of pollutant thresholds. Displacement of mortality on a time scale of one or more years is difficult to infer from ordinary population-based studies because there are a variety of other factors that are also affecting changes in mortality rates. Some long-term changes include demographic changes in the affected population, and changes in the incidence of disease and in cause-specific mortality because of changes in the health care system. The extent to which changes in the relation between mortality rate and air pollution may be confounded with changes in these other factors is uncertain. Prospective studies can in principle account for some of the more important individual risk factors, but the advantage of the prospective design may be lost if changes in individual or personal health risk factors such as smoking status, exercise, habits, and obesity are not included as time-varying covariates in the analyses of the data. These factors may also differ significantly among communities. Long-term changes in mortality could also in principle be detected by changes in air pollution over a shorter time scale than the changes in demographics and in baseline mortality rates.

The chronic exposure studies, taken together, suggest that there may be increases in mortality in disease categories that are consistent with long-term exposure to airborne particles, and that at least some fraction of these deaths are likely to occur between acute exposure episodes. If this interpretation is correct, then at least some individuals may experience some years of reduction of life as a consequence of PM exposure. Unfortunately, without knowing the age and the prior disease state of the decedents, it is not obvious that this information can be usefully quantified.

### **12.7.2 Morbidity Effects of PM Exposure**

Several morbidity health effect endpoints have been studied to examine their association with PM exposure. These studies provide a measure of the respiratory morbidity status of a community in relation to PM exposure. Principle endpoints include hospitalization for a respiratory illness, respiratory symptoms and disease, and changes in lung function. The relationship with these endpoints and PM exposure indicates that ambient exposure to PM impacts the respiratory system. Acute exposure studies show an effect more than chronic exposure studies, but more recent chronic studies are also indicative of an effect. No relationship between acute exposures and chronic health outcomes have been demonstrated.

## *Hospitalization*

Potentially, the most severe morbidity measure is hospitalization for respiratory and cardiovascular illness diagnosis, especially for COPD and pneumonia specifically. This outcome is coherent with the mortality PM relationship discussed above. The hospitalization studies usually compared daily fluctuations in admissions about a long term (e.g., 19 day) moving average. These fluctuations were regressed on PM estimates for the time period immediately preceding or concurrent with the admissions. Some authors considered lags up to 5 days, but the best predictor usually was the most recent exposure. Some morbidity outcomes associated with hospitalization may be appropriately associated with concurrent admission, while others may require several days of progression to end in an admission. Exposure-response lag periods are not yet well examined for hospital admissions related to PM exposures. Both COPD and pneumonia hospitalization studies show moderate but statistically significant relative risks in the range of 1.06 to 1.25 resulting from an increase of  $50 \mu\text{g}/\text{m}^3$  in  $\text{PM}_{10}$  or its equivalent. The admission studies of respiratory and cardiovascular disease show a similar effect. The hospitalization studies in general use similar analysis methodologies. There is evidence of a relationship to heart disease, but the estimated relative risks are somewhat smaller than those for respiratory endpoints. Overall, these studies are indicative of morbidity effects being related to PM exposure (see Figure 12-1).

While a substantive number of hospitalizations for respiratory related illnesses occur in those  $\geq 65$  years of age, there are also numerous hospitalizations for those under 65 years of age. Several of the  $\text{PM}_{10}$  hospitalization studies restricted their analysis by age of the individuals. These studies are clearly indicative of health outcomes related to PM for individuals  $\geq 65$  years of age, but did not explicitly examine other age groups that would allow directly comparable estimates as some mortality studies did. The limited available analyses examining young age groups, especially children  $\leq 14$  years of age, constrain possible conclusions about this age group. Studies by Thurston et al. (1992, 1994a,b) and Burnett et al. (1994, 1995) examining acid aerosols and sulphates however did show results differing by age.

The EPA ozone criteria document (U.S. Environmental Protection Agency, 1996) examines several of these same studies for an  $\text{O}_3$  effect; it concludes that, collectively, the specific studies evaluated indicate that ambient  $\text{O}_3$  often has a significant effect on hospital admissions for asthma and other respiratory causes (with a relative risk ranging from 1.1 to 1.36/100 ppb  $\text{O}_3$ ). The present PM document examines a broader group of studies, which collectively are indicative of

consistent PM effects on hospital admissions for all respiratory causes (COPD, pneumonia, etc.) and for cardiovascular causes. Also, in a very recently reported study which used two pollutant models to evaluate which pollutants made contributions to explaining respiratory hospital admissions, the PM<sub>10</sub> and O<sub>3</sub> associations appeared to be independent of each other, with no reduction in the relative risk for one pollutant after control for the other.

### *Respiratory Illness Studies*

Acute respiratory illness and the factors determining its occurrence and severity are important public health concerns. This effect is of public health importance because of the widespread potential for exposure to PM and because the occurrence of respiratory illness is common. Of added importance is the fact that recurrent childhood respiratory illness may be a risk factor for later susceptibility to lung damage.

The PM studies generally used several different standard respiratory questionnaires that evaluated respiratory health by asking questions about each child's and adult's respiratory disease and symptom experience daily, weekly or over a longer recall period. The reported symptoms and diseases characterize respiratory morbidity in the cohorts studied. Respiratory morbidity typically includes specific diseases such as asthma and bronchitis, and broader syndromes such as upper and lower respiratory illnesses.

Acute respiratory illness studies typically include several different endpoints, but most investigators reported results for at least two of: (1) upper respiratory illness, (2) lower respiratory illness, or (3) cough. The following relative risks are all estimated for an increase of 50 µg/m<sup>3</sup> in PM<sub>10</sub> or its equivalent. The studies of upper respiratory illness do not show a consistent relationship with PM. Two of the studies showed no effect, three studies estimated an odds ratio near 1.2, and one study estimated the odds ratio of 1.55. Some of inconsistency could be explained by the fact that the studies included very different populations. The studies of lower respiratory disease gave odds ratios which ranged from 1.10 to 1.28 except for the Six-Cities study which gave a value over 2.0. Although the lower respiratory disease studies also include a variety of populations, it is difficult to explain the large range of estimates. The studies of cough were more consistent, having odds ratios ranging from 0.98 to 1.51. Again, the Six City study produced the largest value. The second highest value was that of a Utah study at 1.29.

All three endpoints had the same general pattern of results. Nearly all odds ratios were positive, and the 95% confidence intervals for about half were statistically larger than 1.0 (i.e., they were statistically significant at  $p < 0.05$ ). Each endpoint had one study with a very high odds ratio. This can be contrasted with the hospital admission studies, which all resulted in very similar estimates. There are several factors which could account for this. The respiratory disease studies used a wide variety of designs and, as a result, the models for analysis were also varied. Finally, the populations included several different subgroups, whereas the hospitalization studies tended to include similar populations. There were few studies of respiratory symptoms in adults as compared with those in children.

Acute exposures to PM are associated with increased reporting of respiratory symptoms and with small decrements in several measures of lung function. As a consequence, cross-sectional studies of the relationship between long-term exposure to PM (or any air pollutant) and consequent chronic effects on respiratory function and/or respiratory symptoms may be limited by the inability to control for effects of recent exposures on function and symptoms. Moreover, such studies are further handicapped by: (1) limited or no ability to characterize accurately lifetime exposure to PM other than through "area-based" ecological assignments or assignments inferred from short-term, acute measurements; and (2) their inherent limited ability to characterize correctly other relevant exposure histories (e.g., past histories of respiratory illnesses, passive exposure to tobacco smoke products, active smoking in older subjects, etc.).

Longitudinal studies offer numerous obvious advantages over cross-sectional studies in terms of PM exposure characterization and characterization of relevant covariates. Nonetheless, to the extent to which such studies base their inference with regard to the occurrence of long-term morbidity on effects observed over relatively short durations of cohort follow-up (e.g., incident respiratory illness in relationship to ambient PM, short-term relationship between ambient PM and lung function, etc.), their results need to be viewed with circumspection. These approaches do not definitively establish long-term exposure effects but only suggest the coherence of the possibility of such long-term effects.

Three chronic respiratory disease studies were based on a similar type of questionnaire but were done by Harvard University at three different times as part of the Six Cities and 24-Cities Studies. The studies provide data on the relationship of chronic respiratory disease to PM. All three studies suggest a chronic effect of PM on respiratory disease. The analyses for chronic

cough, chest illness and bronchitis tended to be significantly positive. These studies suffer from the usual difficulty of cross sectional studies. The effect of particulate matter is based on variations in exposure which are determined by the different number of locations. The results seen in all studies were consistent with a PM gradient, but it is difficult to separate out clearly the effects of PM versus any other factors or pollutants which have the same gradient. The recent 24 North American City study is strongly suggestive of an effect on bronchitis from acidic particles or from PM which is consistent with the results of the Six Cities study and thus tends to support the gradient observed.

### *Pulmonary Function Studies*

Pulmonary function studies are part of any comprehensive investigation of possible air pollutant effects. Guidelines for standardized testing procedures and for reference values and interpretative strategies of lung function tests exist. Various factors are important determinants of lung function measures. Lung function in childhood is primarily related to age and, especially, to general stature (as measured by height). The growth patterns differ between males and females. Lung function begins to decline with age in the 3rd to 4th decades and continues to do so monotonically as people age. Cigarette smoking, the presence of COPD and, in some cases, asthma are some factors related to more rapid declines in lung function in adults. Environmental factors undoubtedly influence the natural history of the growth and decline of lung function.

Pulmonary function results are somewhat easier to compare because most studies used peak flow (PEFR) or forced expiratory volume (FEV) as the health end-point measure. Acute pulmonary function studies (summarized in Figure 12-6) are suggestive of a short term effect resulting from particulate pollution. Peak flow rates show decreases in the range of 30 to 40 ml/sec resulting from an increase of  $50 \mu\text{g}/\text{m}^3$  in  $\text{PM}_{10}$  or its equivalent. The results appear to be larger in symptomatic groups such as asthmatics. The effects are seen across a variety of study designs, authors, and analysis methodologies. Effects using  $\text{FEV}_1$  or FVC as endpoints are less consistent. For comparison, a study of over 16,000 children found that maternal smoking decreased a child's FEV by 10 - 30 ml. An estimate of the effect of PM on pulmonary function in adults found a  $29 (\pm 10)$  ml decrease in  $\text{FEV}_1$  per  $50 \mu\text{g}/\text{m}^3$  increase in  $\text{PM}_{10}$ , which is similar in magnitude to the changes found in children.

The chronic pulmonary function studies are less numerous than the acute studies. The Six City studies, which had good monitoring data, found no statistically significant PM effect. However, another recent paper found a small but significant decrease in FVC in healthy non-smokers. Yet another recent study is strongly indicative of a PM effect either from acidic particles or from PM itself. Cross sectional studies require very large sample sizes to detect differences because the studies cannot eliminate person to person variation which is much larger than the within person variation. Thus, the lack of statistical significance in some long-term studies cannot be taken as proof of no effect.

Overall, the morbidity studies as a group qualitatively indicate that acute PM exposures are associated with hospitalization admission for respiratory and cardiovascular disease, increased levels of respiratory symptoms and disease, and pulmonary function decrements. The quantitative magnitude of these relationships and their public health meaning are important aspects to consider.

### **12.7.3 Comparison of Human Health Effects of PM<sub>10</sub> Versus PM<sub>2.5</sub> Exposure**

Recent reanalyses of the Six City Study by Schwartz et al. (1996) evaluated the effects of using fine particles (FP = PM<sub>2.5</sub>), inhalable particles (PM<sub>15</sub>), or coarse particles (CP = PM<sub>15</sub> - PM<sub>2.5</sub>) as exposure indices. The results were transformed to standard increments of 25 µg/m<sup>3</sup> PM<sub>2.5</sub> and 50 µg/m<sup>3</sup> PM<sub>15</sub>, and 25 µg/m<sup>3</sup> for CP, with results for short-term (24-h) PM exposures as depicted earlier in Figure 12-33. Across the six cities, PM<sub>2.5</sub> was the most predictive of the three PM indices for daily mortality RR increases except in Steubenville, where a more significant CP effect was found (although the FP effect size was as large as in most other cities). In spite of very considerable differences among the cities in terms of climate and demographics, the FP effect sizes were rather consistent. The CP effect sizes were positive, small, and not significant except in Steubenville (positive, significant) and Topeka (negative, nearly significant). In some cases, CP may need to be considered as well as FP in evaluating PM health risks. Since PM<sub>15</sub> was the sum of FP and CP, it had an intermediate significance, with positive and significant effects except for Portage and Topeka. The St. Louis and Eastern Tennessee associations for PM<sub>15</sub> and FP were both significant, possibly because of the use of nonparametric smoothers to adjust for weather and time trends.

Relationships between chronic PM exposures indexed by different particle size indicators ( $PM_{15}$ ,  $PM_{2.5}$ ,  $PM_{15} - PM_{2.5}$ ) and mortality effects as observed in the Harvard Six City Study were earlier depicted graphically in Figure 12-8. More specifically, the adjusted risks are plotted in Figure 12-8, so as to emphasize the increasing correlation of long-term mortality with PM as the size cut of the particles decreases. The figure shows a modest positive association between RR and TSP, but a stronger association between RR and inhalable particles (IP or  $PM_{15}$ ) and a weaker association between RR and non-inhalable particles (TSP-IP) than between RR and TSP. The figure also shows that there is a stronger association between RR and IP, although the coarse particle relationship is almost linear if Topeka is dropped. The figure also shows that both sulfate and non-sulfate components of fine particles appear to be closely associated with increased PM-related RR.

While numerous morbidity studies have been conducted examining PM health effects for  $PM_{10}$  as discussed above, limited numbers of studies have been published that examine fine particles such as  $PM_{2.5}$ . The most direct comparison of the effect of  $PM_{10}$  to  $PM_{2.5}$  results when studies include both exposure measures in their analyses. For acute exposure studies, this occurred in the Six City study, the Tucson study, and the Uniontown study. None of these studies could directly show that one of these measures was a significantly better predictor than the other. The Six City study suggested that  $PM_{10}$  was a better predictor of respiratory disease. The Tucson study suggested that  $PM_{2.5}$  was a better predictor of lung function change. The Uniontown study used  $PM_{2.5}$ ,  $H^+$ , and  $SO_4^{=}$  values in their analysis, but not  $PM_{10}$  which may have been due to the fact that the  $PM_{10}$  values were not available as 12 h averages whereas the other pollutants were.

Two other studies used  $PM_{2.5}$  as a measure of particulate exposure. A study of respiratory disease in Denver found an effect that fell in the middle of the range of effects found by the  $PM_{10}$  studies. A study of lung function found a slightly larger effect for asthmatics and slightly smaller effect for non-asthmatics when compared with the  $PM_{10}$  studies.

Two recent chronic exposure studies provide results for  $PM_{10}$ ,  $PM_{2.1}$ , and particulate acidity. One respiratory symptoms study in 24 North American communities reported that children living in communities with the highest levels of particle strong acidity were significantly more likely (OR = 1.66, 95% CI = 1.11, 2.48) to report at least one episode of bronchitis in the past year compared to children living in communities with the lowest levels of acidity. For  $PM_{2.1}$ , the odds

ratio for bronchitis was 1.50 (95% CD = 0.91, 2.47). No other respiratory symptoms were significantly associated with any of the pollutants. In particular, there was no evidence that the presence of asthma or asthmatic symptoms was associated with the measured pollutants. No sensitive subgroups were identified. The strong correlations of several pollutants in this study, especially particle strong acidity in the sulfate ( $r = 0.90$ ) and  $PM_{2.1}$  ( $r = 0.82$ ), make it difficult to distinguish the agent of interest.

A study of pulmonary function test results from 22 North American communities described above indicated that a  $52 \text{ nmole/m}^3$  difference in annual mean particle strong acidity was associated with a 3.5% deficit in adjusted FVC and a 3.1% deficit in adjusted  $FEV_1$ . The deficit was larger (but not statistically larger) in lifelong residents of their communities. Deficits were also found in PEFR and MMEFR although these deficits were not statistically significant. Ratios of FEV and FVC were not statistically significant. Slightly smaller deficits were seen using total sulfate,  $PM_{2.1}$ , and  $PM_{10}$  as pollutant exposure measures, and these deficits were also statistically significant. The data did not allow for the separation of effects of the various particulate matter exposures.

These few studies on  $PM_{2.5}$  show effects that are difficult to separate both from  $PM_{10}$  measures and acid aerosols measures which are briefly discussed in the next section. The  $PM_{2.5}$  studies do show effects related to exposure to the fine fraction. The high correlation between  $PM_{2.5}$ ,  $PM_{10}$ , and acid aerosols may make it very difficult to separate out differences.

### ***Health Effects of Acid Aerosols***

While most epidemiology studies of PM measure or estimate mass of PM, several studies measured the mass of acid aerosols. Presently this represents the main chemical characterization of PM. However, this mass would primarily be found in the fine fraction of PM, that is  $PM_{2.5}$ .

Earlier and present-day studies suggest that there can be both acute and chronic effects by strongly acidic PM on human health. Studies of historical pollution for episodes, notably the London Fog episodes of the 1950's and early 1960's, indicate that extremely elevated daily acid aerosol concentrations may be associated with excess acute human mortality when present as a co-pollutant with elevated concentrations of PM and  $SO_2$ . In addition, significant associations were found between acid aerosols and mortality in London during non-episode pollution levels ( $\leq 7.5 \mu\text{g/m}^3$  as  $H_2SO_4$ , or  $\leq$  approximately  $150 \text{ nmole/m}^3 H^+$ ), though these associations could not

be separated from those for BS or SO<sub>2</sub> (Lippman and Ito, 1995). The attempts to-date to associate present-day levels of acidic aerosols with acute and chronic mortality were unable to do so, but there may not have been a sufficiently long series of H<sup>+</sup> data to detect H<sup>+</sup> associations. Increased hospital admissions for respiratory causes were also documented during the London Fog episode of 1952, and this association has now been observed under present-day conditions, as well. In these studies, H<sup>+</sup> effects were estimated to be the largest during 1 to 3-day acid aerosol episodes (H<sup>+</sup> ≥ 10 μg/m<sup>3</sup> as H<sub>2</sub>SO<sub>4</sub>, or ≈200 nmoles/m<sup>3</sup> H<sup>+</sup>), which occur roughly 2 to 3 times per year in eastern North America. These studies suggest that present-day strongly acidic aerosols can represent a portion of PM which is particularly associated with significant acute respiratory disease health effects in the general public.

Results from recent acute symptoms and lung function studies of healthy children indicate the potential for acute acidic PM effects in this population. The 6-City study of diaries kept by parents of children's respiratory and other illness show H<sup>+</sup> associations with lower respiratory symptoms at H<sup>+</sup> above 110 moles/m<sup>3</sup>. Some, but not all, recent summer camp and school children studies of lung function have also indicated significant associations between acute exposures to acidic PM and decreases in the lung function of children independent of those associated with O<sub>3</sub>.

Studies of the effects of chronic H<sup>+</sup> exposures on children's respiratory symptoms and lung function are generally suggestive of effects due to chronic H<sup>+</sup> exposure. Preliminary analyses of bronchitis prevalence rates as reported across the 6-City study locales were found to be more closely associated with average H<sup>+</sup> concentrations than with PM in general. Furthermore, in a study of children in 24 U.S. and Canadian communities in which the analysis was adjusted for the effects of gender, age, parental asthma, parental education, and parental allergies, bronchitic symptoms were confirmed to be significantly associated with strongly acidic PM (relative odds = 1.66, 95% CI: 1.11 to 2.48). It was also found in the 24-Cities study that mean FVC and FEV<sub>1.0</sub> were lower in locales having high particle strong acidity. Thus, chronic exposures to strongly acidic PM may have effects on measures of respiratory health in children. The acid levels, however, were highly correlated to other PM indicators such as PM<sub>2.1</sub>, as noted above.

## REFERENCES

- Abbey, D. E.; Mills, P. K.; Petersen, F. F.; Beeson, W. L. (1991a) Long-term ambient concentrations of total suspended particulates and oxidants as related to incidence of chronic disease in California Seventh-Day Adventists. *Environ. Health Perspect.* 94: 43-50.
- Abbey, D. E.; Moore, J.; Petersen, F.; Beeson, L. (1991b) Estimating cumulative ambient concentrations of air pollutants: description and precision of methods used for an epidemiological study. *Arch. Environ. Health* 46: 281-287.
- Abbey, D. E.; Petersen, F.; Mills, P. K.; Beeson, W. L. (1993) Long-term ambient concentrations of total suspended particulates, ozone, and sulfur dioxide and respiratory symptoms in a nonsmoking population. *Arch. Environ. Health* 48: 33-46.
- Abbey, D. E.; Lebowitz, M. D.; Mills, P. K.; Petersen, F. F.; Beeson, W. L.; Burchette, R. J. (1995a) Long-term ambient concentrations of particulates and oxidants and development of chronic disease in a cohort of nonsmoking California residents. In: Phalen, R. F.; Bates, D. V., eds. *Proceedings of the colloquium on particulate air pollution and human mortality and morbidity*; January 1994; Irvine, CA. *Inhalation Toxicol.* 7: 19-34.
- Abbey, D. E.; Ostro, B. E.; Petersen, F.; Burchette, R. J. (1995b) Chronic respiratory symptoms associated with estimated long-term ambient concentrations of fine particulates less than 2.5 microns in aerodynamic diameter (PM<sub>2.5</sub>) and other air pollutants. *J. Exp. Anal. Environ. Epidemiol.* 5: 137-159.
- Abbey, D. E.; Ostro, B. E.; Fraser, G.; Vancuren, T.; Burchette, R. J. (1995c) Estimating fine particulates less than 2.5 microns in aerodynamic diameter (PM<sub>2.5</sub>) from airport visibility data in California. *J. Exp. Anal. Environ. Epidemiol.* 5: 161-180.
- Ackermann-Lieblich, U.; Leuenberger, P.; Schwartz, J.; Schindler, C.; Monn, C.; Bolognini, B.; Bongard, J. P.; Brändli, O.; Domenighetti, G.; Elsasser, S.; Grize, L.; Karrer, W.; Keller, R.; Keller-Wossidlo, H.; Künzli, N.; Martin, B. W.; Medici, T. G.; Perruchoud, A. P.; Schöni, M. H.; Tschopp, J. M.; Villiger, B.; Wüthrich, B.; Zellweger, J. P.; Zemp, E. (1996) Lung function and long term exposure to air pollutants in Switzerland. *Am. J. Respir. Crit. Care Med*: submitted.
- Akaike, H. (1973) Information theory and an extension of the maximum likelihood principle. In: Petrov, B. N.; Csáki, F., eds. *2nd International symposium on information theory*; September 1971; Tsahkadsor, Armenia, USSR. Budapest, Hungary: Akadémiai Kiadó; pp. 267-281.
- American Thoracic Society. (1962) Definitions and classification of chronic bronchitis, asthma, and pulmonary emphysema. *Am. Rev. Respir. Dis.* 85: 762-768.
- American Thoracic Society. (1987) Standardization of spirometry—1987 update. *Am. Rev. Respir. Dis.* 136: 1285-1298.
- American Thoracic Society. (1991) Lung function testing: selection of reference values and interpretative strategies *Am. Rev. Respir. Dis.* 144: 1202-1218.
- Anderson, D. O.; Ferris, B. G., Jr. (1965) Air pollution levels and chronic respiratory disease. *Arch. Environ. Health* 10: 307-311.
- Anderson, D. O.; Ferris, B. G., Jr.; Zickmantel, R. (1964) Levels of air pollution and respiratory disease in Berlin, New Hampshire. *Am. Rev. Respir. Dis.* 90: 877-887.
- Arossa, W.; Spinaci, S.; Bugiani, M.; Natale, P.; Bucca, C.; de Candussio, G. (1987) Changes in lung function of children after an air pollution decrease. *Arch. Environ. Health* 42: 170-174.
- Bailey, D. L. R.; Clayton, P. (1982) The measurement of suspended particle and total carbon concentrations in the atmosphere using standard smoke shade methods. *Atmos. Environ.* 16: 2683-2690.

- Bates, D. V. (1992) Health indices of the adverse effects of air pollution: the question of coherence. *Environ. Res.* 59: 336-349.
- Bates, D. V.; Sizto, R. (1983) Relationship between air pollutant levels and hospital admissions in Southern Ontario. *Can. J. Public Health* 74: 117-122.
- Bates, D. V.; Sizto, R. (1986) A study of hospital admissions and air pollutants in southern Ontario. In: Lee, S. D.; Schneider, T.; Grant, L. D.; Verkerk, P. J., eds. *Aerosols: research, risk assessment and control strategies, proceedings of the second U.S.-Dutch international symposium; May 1985; Williamsburg, VA.* Chelsea, MI: Lewis Publishers, Inc.; pp. 767-777.
- Bates, D. V.; Sizto, R. (1987) Air pollution and hospital admissions in southern Ontario: the acid summer haze effect. *Environ. Res.* 43: 317-331.
- Bates, D. V.; Sizto, R. (1989) The Ontario Air Pollution study: identification of the causative agent. *Environ. Health Perspect.* 79: 69-72.
- Beard, C. M.; Yunginger, J. W.; Reed, C. E.; O'Connell, E. J.; Silverstein, M. D. (1992) Interobserver variability in medical record review: an epidemiological study of asthma. *J. Clin. Epidemiol.* 45: 1013-1020.
- Beaumont, J. J.; Leveton, J.; Knox, K.; Bloom, T.; McQuiston, T.; Young, M.; Goldsmith, R.; Steenland, N. K.; Brown, D. P.; Halpern, W. E. (1987) Lung cancer mortality in workers exposed to sulfuric acid mist and other acid mists. *JNCI J. Natl. Cancer Inst.* 79: 911-921.
- Belloc, N. D. (1973) Relationship of health practices and mortality. *Prev. Med.* 2: 67-81.
- Belsley, D. A.; Kuh, E.; Welsch, R. E. (1980) *Regression diagnostics: identifying influential data and sources of collinearity.* New York, NY: John Wiley & Sons, Inc. (Bradley, R. A.; Kendall, D. G.; Hunter, J. S.; Watson, G. S., eds. *Wiley series in probability and mathematical statistics*).
- Bobak, M.; Leon, D. A. (1992) Air pollution and infant mortality in the Czech Republic, 1986-1988. *Lancet* (8826): 1010-1014.
- Bock, N.; Lippmann, M.; Liroy, P.; Munoz, A.; Speizer, F. E. (1985) The effects of ozone on the pulmonary function of children. In: Lee, S. D., ed. *Evaluation of the scientific basis for ozone/oxidants standards: proceedings of an APCA international specialty conference; November 1984; Houston, TX.* Pittsburgh, PA: Air Pollution Control Association; pp. 297-308. (APCA international specialty conference transactions: TR-4).
- Bouhuys, A.; Beck, G. J.; Schoenberg, J. B. (1978) Do present levels of air pollution outdoors affect respiratory health? *Nature (London)* 276: 466-471.
- Box, G. E. P.; Jenkins, G. M. (1976) *Time series analysis: forecasting and control.* San Francisco, CA: Holden-Day. (Robinson, E., ed. *Holden-Day series in time series analysis and digital processing*).
- Brancati, F. L.; Chow, J. W.; Wagener, M. M.; Vacarello, S. J.; Yu, V. L. (1993) Is pneumonia really the old man's friend? Two-year prognosis after community-acquired pneumonia. *Lancet* (8862): 30-33.
- Braun-Fahrlander, C.; Ackermann-Lieblich, U.; Schwartz, J.; Gnehm, H. P.; Rutishauser, M.; Wanner, H. U. (1992) Air pollution and respiratory symptoms in preschool children. *Am. Rev. Respir. Dis.* 145: 42-47.
- Britten, N.; Davies, J. M. C.; Colley, J. R. T. (1987) Early respiratory experience and subsequent cough and peak expiratory flow rate in 36 year old men and women. *Br. Med. J.* 294: 1317-1320.

- Brunekeerf, B.; Kinney, P. L.; Ware, J. H.; Dockery, D.; Speizer, F. E.; Spengler, J. D.; Ferris, B. G., Jr. (1991) Sensitive subgroups and normal variation in pulmonary function response to air pollution episodes. *Environ. Health Perspect.* 90: 189-193.
- Buffington, J.; Chapman, L. E.; Schmeltz, L. M.; Kendal, A. P. (1993) Do family physicians make good sentinels for influenza? *Arch. Fam. Med.* 2: 859-865.
- Burnett, R. T.; Dales, R. E.; Raizenne, M. E.; Krewski, D.; Summers, P. W.; Roberts, G. R.; Raad-Young, M.; Dann, T.; Brook, J. (1994) Effects of low ambient levels of ozone and sulfates on the frequency of respiratory admissions to Ontario hospitals. *Environ. Res.* 65: 172-194.
- Burnett, R. T.; Dales, R.; Krewski, D.; Vincent, R.; Dann, T.; Brook, J. R. (1995) Associations between ambient particulate sulfate and admissions to Ontario hospitals for cardiac and respiratory diseases. *Am. J. Epidemiol.* 142: 15-22.
- Burrows, B.; Lebowitz, M. D. (1975) Characteristics of chronic bronchitis in a warm, dry region. *Am. Rev. Respir. Dis.* 112: 365-370.
- Burton, R. M.; Suh, H. H.; Koutrakis, P. (1996) Spatial variation in particulate concentrations within metropolitan Philadelphia. *Environ. Sci. Technol.* 30: 400-407.
- Carr, W.; Zeitel, L.; Weiss, K. (1992) Variations in asthma hospitalizations and deaths in New York City. *Am. J. Public Health* 82: 59-65.
- Cass, G. R.; Conklin, M. H.; Shah, J. J.; Huntzicker, J. J.; Macias, E. S. (1984) Elemental carbon concentrations: estimation of an historical data base. *Atmos. Environ.* 18: 153-162.
- Chanock, R. M.; Parrott, R. H. (1965) Acute respiratory disease in infancy and childhood: present understanding and prospects for prevention. *Pediatrics* 36: 21-39.
- Chanock, R. M.; McIntosh, K.; Murphy, B. R.; Parrott, R. H. (1989) Respiratory syncytial virus. In: Evans, A. S., ed. *Viral infections of humans: epidemiology and control*. 3rd ed. New York, NY: Plenum Publishing Corporation; pp. 525-544.
- Chapman, R. S.; Henderson, F. W.; Clyde, W. A., Jr.; Collier, A. M.; Denny, F. W. (1981) The epidemiology of tracheobronchitis in pediatric practice. *Am. J. Epidemiol.* 114: 786-797.
- Chapman, R. S.; Calafiore, D. C.; Hasselblad, V. (1985) Prevalence of persistent cough and phlegm in young adults in relation to long-term ambient sulfur oxide exposure. *Am. Rev. Respir. Dis.* 132: 261-267.
- Chappie, M.; Lave, L. (1982) The health effects of air pollution: a reanalysis. *J. Urban Econ.* 12: 346-376.
- Charlton, A.; Blair, V. (1989) Absence from school related to children's and parental smoking habits. *Br. Med. J.* 298: 90-92.
- Chestnut, L. G.; Schwartz, J.; Savitz, D. A.; Burchfiel, C. M. (1991) Pulmonary function and ambient particulate matter: epidemiological evidence from NHANES I. *Arch. Environ. Health* 46: 135-144.
- Cifuentes, L.; Lave, L. B. (1996) Association of daily mortality and air pollution in Philadelphia, 1983-1988. *J. Air Waste Manage. Assoc.*: in press.
- Cleveland, W. S. (1979) Robust locally weighted regression and smoothing scatterplots. *J. Am. Stat. Assoc.* 74: 829-836.
- Cochran, W. G. (1968) Errors of measurement in statistics. *Technometrics* 10: 637-666.

- Cohen, B. L. (1994) Invited commentary: in defense of ecologic studies for testing a linear-no threshold theory. *Am. J. Epidemiol.* 139: 765-768.
- Commins, B. T. (1963) Determination of particulate acid in town air. *Analyst (London)* 88: 364-367.
- Commins, B. T.; Waller, R. E. (1967) Observations from a ten-year-study of pollution at a site in the city of London. *Atmos. Environ.* 1: 49-68.
- Cooper, D. E.; Hamilton, W. C. (1979) Atmospheric sulfates and mortality—the phantom connection. *Min. Congr. J.* 65(1): 49-55.
- Cox, C. (1987) Threshold dose-response models in toxicology. *Biometrics* 43: 511-523.
- Crane, J.; Pearce, N.; Burgess, C.; Woodman, K.; Robson, B.; Beasley, R. (1992) Markers of risk of asthma death or readmission in the 12 months following a hospital admission for asthma. *Int. J. Epidemiol.* 21: 737-744.
- Crump, K. S. (1984a) A new method for determining allowable daily intakes. *Fundam. Appl. Toxicol.* 4: 854-871.
- Crump, K. S. (1984b) Mechanisms leading to dose-response models. In: Ficci, P. F., ed. *Principles of health risk assessment*. Englewood Cliffs, NJ: Prentice-Hall, Inc.; pp. 235-277.
- Crump, K. S.; Howe, R. B. (1985) A review of methods for calculating statistical confidence limits in low dose extrapolation. In: Clayson, D. B.; Krewski, D.; Munro, I., eds. *Toxicological risk assessment: v. I, biological and statistical criteria*. Boca Raton, FL: CRC Press, Inc.; pp. 187-203.
- Damokosh, A. I.; Spengler, J. D.; Dockery, D. W.; Ware, J. H.; Speizer, F. E. (1993) Effects of acidic particles on respiratory symptoms in 7 US communities. *Am. Rev. Respir. Dis.* 147: A632.
- Dassen, W.; Brunekreef, B.; Hoek, G.; Hofschreuder, P.; Staatsen, B.; De Groot, H.; Schouten, E.; Biersteker, K. (1986) Decline in children's pulmonary function during an air pollution episode. *J. Air Pollut. Control Assoc.* 36: 1223-1227.
- Delfino, R. J.; Becklake, M. R.; Hanley, J. A. (1994a) The relationship of urgent hospital admissions for respiratory illnesses to photochemical air pollution levels in Montreal. *Environ. Res.* 67: 1-19.
- Delfino, R. J.; Becklake, M. R.; Hanley, J. A.; Singh, B. (1994b) Estimation of unmeasured particulate air pollution data for an epidemiological study of daily respiratory morbidity. *Environ. Res.* 67: 20-38.
- Denny, F. W.; Clyde, W. A. (1986) Acute lower respiratory tract infections in nonhospitalized children. *J. Pediatr. (St. Louis)* 108: 635-646.
- Denny, F. W.; Murphy, T. F.; Clyde, W. A., Jr.; Collier, A. M.; Henderson, F. W. (1983) Croup: an 11-year study in a pediatric practice. *Pediatrics* 71: 871-876.
- Derriennic, F.; Richardson, S.; Mollie, A.; Lellouch, J. (1989) Short-term effects of sulphur dioxide pollution on mortality in two French cities. *Int. J. Epidemiol.* 18: 186-197.
- Dinman, B. D. (1972) "Non-concept" of "no-threshold": chemicals in the environment. *Science (Washington, DC)* 175: 495-497.
- Dockery, D. W. (1993) Epidemiological study design for investigating respiratory health effects of complex air pollution mixtures. *Environ. Health Perspect.* 101(suppl. 4): 187-191.
- Dockery, D. W. (1995) Particle/mortality associations in St. Louis and eastern Tennessee: elaboration of published results. Prepared for: EPA critical evaluation workshop on particulate matter-mortality epidemiology studies;

November 1994; Raleigh, NC. Boston, MA: Harvard School of Public Health, Department of Environmental Health.

- Dockery, D. W.; Pope, C. A., III. (1994a) Air pollution and mortality: the authors reply [letter]. *N. Engl. J. Med.* 330: 1238.
- Dockery, D. W.; Pope, C. A., III. (1994b) Acute respiratory effects of particulate air pollution. *Annu. Rev. Public Health* 15: 107-132.
- Dockery, D. W.; Schwartz, J. (1992) The authors' response to Waller and Swan. *Am. J. Epidemiol.* 135: 23-25.
- Dockery, D. W.; Ware, J. H.; Ferris, B. G., Jr.; Speizer, F. E.; Cook, N. R.; Herman, S. M. (1982) Change in pulmonary function in children associated with air pollution episodes. *J. Air Pollut. Control Assoc.* 32: 937-942.
- Dockery, D. W.; Berkey, C. S.; Ware, J. H.; Speizer, F. E.; Ferris, B. G., Jr. (1983) Distribution of forced vital capacity and forced expiratory volume in one second in children 6 to 11 years of age. *Am. Rev. Respir. Dis.* 128: 405-412.
- Dockery, D. W.; Ware, J. H.; Ferris, B. G., Jr.; Glicksberg, D. S.; Fay, M. E.; Spiro, A., III; Speizer, F. E. (1985) Distribution of forced expiratory volume in one second and forced vital capacity in healthy, white, adult never-smokers in six U.S. cities. *Am. Rev. Respir. Dis.* 131: 511-520.
- Dockery, D. W.; Speizer, F. E.; Stram, D. O.; Ware, J. H.; Spengler, J. D.; Ferris, B. G., Jr. (1989) Effects of inhalable particles on respiratory health of children. *Am. Rev. Respir. Dis.* 139: 587-594.
- Dockery, D. W.; Schwartz, J.; Spengler, J. D. (1992) Air pollution and daily mortality: associations with particulates and acid aerosols. *Environ. Res.* 59: 362-373.
- Dockery, D. W.; Pope, C. A., III; Xu, X.; Spengler, J. D.; Ware, J. H.; Fay, M. E.; Ferris, B. G., Jr.; Speizer, F. E. (1993) An association between air pollution and mortality in six U.S. cities. *N. Engl. J. Med.* 329: 1753-1759.
- Dockery, D. W.; Cunningham, J.; Damokosh, A. I.; Neas, L. M.; Spengler, J. D.; Koutrakis, P.; Ware, J. H.; Raizenne, M.; Speizer, F. E. (1996) Health effects of acid aerosols on North American children: respiratory symptoms. *Environ. Health Perspect.* in press.
- Dodge, R.; Solomon, P.; Moyers, J.; Hayes, C. (1985) A longitudinal study of children exposed to sulfur oxides. *Am. J. Epidemiol.* 121: 720-736.
- Doll, R.; Peto, R.; Hall, E.; Wheatley, K.; Gray, R. (1994) Mortality in relation to consumption of alcohol: 13 years' observations on male British doctors. *Br. Med. J.* 309: 911-918.
- Duclos, P.; Sanderson, L. M.; Lipsett, M. (1990) The 1987 forest fire disaster in California: assessment of emergency room visits. *Arch. Environ. Health* 45: 53-58.
- Dusseldorp, A.; Kruize, H.; Brunekreef, B.; Hofschreuder, P.; de Meer, G.; van Oudvorst, A. B. (1994) Associations of PM10 and airborne iron with respiratory health of adults living near a steel factory. *Am. J. Respir. Crit. Care Med.* 152: 1932-1939.
- Euler, G. L.; Abbey, D. E.; Magie, A. R.; Hodgkin, J. E. (1987) Chronic obstructive pulmonary disease symptom effects of long-term cumulative exposure to ambient levels of total suspended particulates and sulfur dioxide in California Seventh-Day Adventist residents. *Arch. Environ. Health* 42: 213-222.
- Euler, G. L.; Abbey, D. E.; Hodgkin, J. E.; Magie, A. R. (1988) Chronic obstructive pulmonary disease symptom effects of long-term cumulative exposure to ambient levels of total oxidants and nitrogen dioxide in California Seventh-day Adventist residents. *Arch. Environ. Health* 43: 279-285.

- European Myocardial Infarction Project Group. (1993) Prehospital thrombolytic therapy in patients with suspected acute myocardial infarction. *N. Engl. J. Med.* 329: 383-389.
- Evans, J. S.; Tosteson, T.; Kinney, P. L. (1984a) Cross-sectional mortality studies and air pollution risk assessment. *Environ. Int.* 10: 55-83.
- Evans, J. S.; Kinney, P. L.; Koehler, J. L.; Cooper, D. W. (1984b) The relationship between cross-sectional and time series studies. *J. Air Pollut. Control Assoc.* 34: 551-553.
- Fairley, D. (1990) The relationship of daily mortality to suspended particulates in Santa Clara county, 1980-86. *Environ. Health Perspect.* 89: 159-168.
- Fairley, D. (1994) Mortality and particulate exposure in Santa Clara County, CA 1980-86. Santa Clara, CA: Bay Area Air Quality Management District.
- Federal Register. (1987) Revisions to the national ambient air quality standards for particulate matter. *F. R.* (July 1) 52: 24634-24669.
- Fedson, D. S.; Wajda, A.; Nicol, J. P.; Roos, L. L. (1992) Disparity between influenza vaccination rates and risks for influenza-associated hospital discharge and death in Manitoba in 1982-1983. *Ann. Intern. Med.* 116: 550-555.
- Ferrand, E. (1978) Air quality trends in New York City. *Bull. N.Y. Acad. Med.* 54: 1025-1031.
- Ferris, B. G., Jr.; Anderson, D. O. (1962) The prevalence of chronic respiratory disease in a New Hampshire town. *Am. Rev. Respir. Dis.* 86: 165-185.
- Ferris, B. G., Jr.; Burgess, W. A.; Worcester, J. (1967) Prevalence of chronic respiratory disease in a pulp mill and a paper mill in the United States. *Br. J. Ind. Med.* 24: 26-37.
- Ferris, B. G., Jr.; Higgins, I. T. T.; Higgins, M. W.; Peters, J. M.; Van Ganse, W. F.; Goldman, M. D. (1971) Chronic nonspecific respiratory disease, Berlin, New Hampshire, 1961-1967: a cross-sectional study. *Am. Rev. Respir. Dis.* 104: 232-244.
- Ferris, B. G., Jr.; Chen, H.; Puleo, S.; Murphy, R. L. H., Jr. (1976) Chronic nonspecific respiratory disease in Berlin, New Hampshire, 1967 to 1973: a further follow-up study. *Am. Rev. Respir. Dis.* 113: 475-485.
- Ferris, B. G., Jr.; Speizer, F. E.; Spengler, J. D.; Dockery, D.; Bishop, Y. M. M.; Wolfson, M.; Humble, C. (1979) Effects of sulfur oxides and respirable particles on human health: methodology and demography of populations in study. *Am. Rev. Respir. Dis.* 120: 767-779.
- Ferris, B. G., Jr.; Ware, J. H.; Spengler, J. D.; Dockery, D. W.; Speizer, F. E. (1986) The Harvard six-cities study. In: Lee, S. D.; Schneider, T.; Grant, L. D.; Verkerk, P. J., eds. *Aerosols: research, risk assessment and control strategies: proceedings of the second U.S.-Dutch international symposium; May 1985; Williamsburg, VA.* Chelsea, MI: Lewis Publishers, Inc.; pp. 721-730.
- Firket, J. (1931) Sur les causes des accidents survenus dans la vallée de la Meuse, lors des brouillards de décembre 1930 [The causes of accidents which occurred in the Meuse Valley during the fogs of December 1930]. *Bull. Acad. R. Med. Belg.* 11[ser. 5]: 683-741.
- Firket, J. (1936) Fog along the Meuse Valley. *Trans. Faraday Soc.* 32: 1192-1197.
- Franklin, C. A.; Burnett, R. T.; Paolini, R. J. P.; Raizenne, M. E. (1985) Health risks from acid rain: a Canadian perspective. *Environ. Health Perspect.* 63: 155-168.

- Gamble, J.; Jones, W.; Hancock, J. (1984a) Epidemiological-environmental study of lead acid battery workers: II. acute effects of sulfuric acid on the respiratory system. *Environ. Res.* 35: 11-29.
- Gamble, J.; Jones, W.; Hancock, J.; Meckstroth, R. L. (1984b) Epidemiological-environmental study of lead acid battery workers: III. chronic effects of sulfuric acid on the respiratory system and teeth. *Environ. Res.* 35: 30-52.
- Gergen, P. J.; Weiss, K. B. (1990) Changing patterns of asthma hospitalization among children: 1979 to 1987. *JAMA J. Am. Med. Assoc.* 264: 1688-1692.
- Gerstman, B. B.; Bosco, L. A.; Tomita, D. K. (1993) Trends in the prevalence of asthma hospitalization in the 5- to 14-year-old Michigan Medicaid population, 1980 to 1986. *J. Allergy Clin. Immunol.* 91: 838-843.
- Gilbert, E. S. (1984) Some effects of random dose measurement errors on analyses of atomic bomb survivor data. *Radiat. Res.* 98: 591-605.
- Glezen, W. P. (1989) Antecedents of chronic and recurrent lung disease: childhood respiratory trouble. *Am. Rev. Respir. Dis.* 140: 873-874.
- Glezen, W. P.; Denny, F. W. (1973) Epidemiology of acute lower respiratory disease in children. *N. Engl. J. Med.* 288: 498-505.
- Gold, D. R.; Tager, I. B.; Weiss, S. T.; Tosteson, T. D.; Speizer, F. E. (1989) Acute lower respiratory illness in childhood as a predictor of lung function and chronic respiratory symptoms. *Am. Rev. Respir. Dis.* 140: 877-884.
- Gordian, M. E.; Morris, S.; Özkaynak, H.; Xue, J.; Spengler, J. (1995) Particulate air pollution and respiratory disease in Anchorage, Alaska. In: *Particulate matter: health and regulatory issues: proceedings of an international specialty conference; April; Pittsburgh, PA. Pittsburgh, PA: Air & Waste Management Association; pp. 143-166. (A&WMA publication VIP-49).*
- Gordian, M. E.; Özkaynak, H.; Xue, J.; Morris, S. S.; Spengler, J. D. (1996) Particulate air pollution and respiratory disease in Anchorage, Alaska. *Environ. Health Perspect.* 104: 209-297.
- Greenland, S.; Robins, J. (1994a) Invited commentary: ecologic studies—biases, misconceptions, and counterexamples. *Am. J. Epidemiol.* 139: 747-760.
- Greenland, S.; Robins, J. (1994b) Accepting the limits of ecologic studies: Drs. Greenland and Robins reply to Drs. Piantadosi and Cohen. *Am. J. Epidemiol.* 139: 769-771.
- Greenland, S.; Schlesselman, J. J.; Criqui, M. H. (1986) The fallacy of employing standardized regression coefficients and correlations as measures of effect. *Am. J. Epidemiol.* 123: 203-208.
- Grønbæk, M.; Deis, A.; Sørensen, T. I. A.; Becker, U.; Borch-Johnsen, K.; Müller, C.; Schnohr, P.; Jensen, G. (1994) Influence of sex, age, body mass index, and smoking on alcohol intake and mortality. *Br. Med. J.* 308: 302-306.
- Hasselblad, V.; Creason, J. P.; Nelson, C. J. (1976) Regression using "hockey stick" function. Research Triangle Park, NC: U.S. Environmental Protection Agency, Health Effects Research Laboratory; EPA report no. EPA-600/1-76-024. Available from: NTIS, Springfield, VA; PB-253 576.
- Hasselblad, V.; Humble, C. G.; Graham, M. G.; Anderson, H. S. (1981) Indoor environmental determinants of lung function in children. *Am. Rev. Respir. Dis.* 123: 479-485.
- Hasselblad, V.; Eddy, D. M.; Kotchmar, D. J. (1992) Synthesis of environmental evidence: nitrogen dioxide epidemiology studies. *J. Air Waste Manage. Assoc.* 42: 662-671.
- Hastie, T.; Tibshirani, R. (1990) *Generalized additive models.* London, United Kingdom: Chapman and Hall.

- Hausman, J. A.; Ostro, B. D.; Wise, D. A. (1984) Air pollution and lost work. Cambridge, MA: National Bureau of Economic Research; NBER working paper no. 1263.
- He, Q.-C.; Lioy, P. J.; Wilson, W. E.; Chapman, R. S. (1993) Effects of air pollution on children's pulmonary function in urban and suburban areas of Wuhan, People's Republic of China. *Arch. Environ. Health* 48: 382-391.
- Hefflin, B. J.; Jalaludin, B.; McClure, E.; Cobb, N.; Johnson, C. A.; Jecha, L.; Etzel, R. A. (1994) Surveillance for dust storms and respiratory diseases in Washington State, 1991. *Arch. Environ. Health* 49: 170-174.
- Hemeon, W. C. L. (1955) The estimation of health hazards from air pollution. *AMA Arch. Ind. Health* 11: 397-402.
- Henderson, F. W.; Clyde, W. A., Jr.; Collier, A. M.; Denny, F. W.; Senior, R. J.; Sheaffer, C. I.; Conley, W. G., III; Christian, R. M. (1979a) The etiologic and epidemiologic spectrum of bronchiolitis in pediatric practice. *J. Pediatr. (St. Louis)* 95: 183-190.
- Henderson, F. W.; Collier, A. M.; Clyde, W. A., Jr.; Denny, F. W. (1979b) Respiratory-syncytial-virus infections, reinfections and immunity: a prospective, longitudinal study in young children. *N. Engl. J. Med.* 300: 530-534.
- Hill, A. B. (1965) The environment and disease: association or causation? *Proc. R. Soc. Med.* 58: 295-300.
- Hochberg, Y.; Tamhane, A. C. (1987) Multiple comparison procedures. New York, NY: John Wiley & Sons, Inc.; pp. 17-133.
- Hodgkin, J. E.; Abbey, D. E.; Euler, G. L.; Magie, A. R. (1984) COPD prevalence in nonsmokers in high and low photochemical air pollution areas. *Chest* 86: 830-838.
- Hoek, G. (1992) Acute effects of ambient air pollution episodes on respiratory health of children [thesis]. Wageningen, The Netherlands: Agricultural University of Wageningen.
- Hoek, G.; Brunekreef, B. (1993) Acute effects of a winter air pollution episode on pulmonary function and respiratory symptoms of children. *Arch. Environ. Health* 48: 328-335.
- Hoek, G.; Brunekreef, B. (1994) Effects of low-level winter air pollution concentrations on respiratory health of Dutch children. *Environ. Res.* 64: 136-150.
- Hoek, G.; Brunekreef, B. (1995) Effect of photochemical air pollution on acute respiratory symptoms in children. *Am. J. Respir. Crit. Care Med.* 151: 27-32.
- Hudson, D. J. (1966) Fitting segmented curves whose join points have to be estimated. *J. Am. Stat. Assoc.* 61: 1097-1129.
- Hunter, J. E.; Schmidt, F. L. (1989) Methods of meta-analysis: correcting error & bias in research findings. Thousand Oaks, CA: Sage Publications, Inc.
- International Electric Research Exchange. (1981) Effects of SO<sub>2</sub> and its derivatives on health and ecology: volume I, human health. Palo Alto, CA: Electrical Power Research Institute.
- Ishikawa, S.; Bowden, D. H.; Fisher, V.; Wyatt, J. P. (1969) The "emphysema profile" in two midwestern cities in North America. *Arch. Environ. Health* 18: 660-666.
- Ito, K. (1990) An examination of the role of aerosol acidity in historical London, England daily mortality [dissertation]. Syracuse, NY: New York University. Available from: University Microfilms International, Ann Arbor, MI; AAD91-13012.

- Ito, K.; Thurston, G. D. (1996) Daily PM<sub>10</sub>/mortality associations: an investigation of at-risk sub-populations. *J. Exposure Anal. Environ. Epidemiol.*: in press.
- Ito, K.; Thurston, G. D.; Hayes, C.; Lippmann, M. (1993) Associations of London, England, daily mortality with particulate matter, sulfur dioxide, and acidic aerosol pollution. *Arch. Environ. Health* 48: 213-220.
- Ito, K.; Kinney, P.; Thurston, G. D. (1995) Variations in PM-10 concentrations within two metropolitan areas and their implications for health effects analyses. In: Phalen, R. F.; Bates, D. V., eds. *Proceedings of the colloquium on particulate air pollution and human mortality and morbidity, part II*; January 1994; Irvine, CA. *Inhalation Toxicol.* 7: 735-745.
- Jedrychowski, W.; Krzyżanowski, M. (1989) Ventilatory lung function and chronic chest symptoms among the inhabitants of urban areas with various levels of acid aerosols: prospective study in Cracow. In: *Symposium on the health effects of acid aerosols*; October 1987; Research Triangle Park, NC. *Environ. Health Perspect.* 79: 101-107.
- Jedrychowski, W.; Becher, H.; Wahrendorf, J.; Basa-Cierpielek, Z. (1990) A case-control study of lung cancer with special reference to the effect of air pollution in Poland. *J. Epidemiol. Commun. Health* 44: 114-120.
- Jenkins, J. S.; Flaker, G. C.; Nolte, B.; Price, L. A.; Morris, D.; Kurz, J.; Petroski, G. F. (1994) Causes of higher in-hospital mortality in women than in men after acute myocardial infarction. *Am. J. Cardiol.* 73: 319-322.
- Johnson, K. G.; Loftsgaarden, D. O.; Gideon, R. A. (1982) The effects of Mount St. Helens volcanic ash on the pulmonary function of 120 elementary school children. *Am. Rev. Respir. Dis.* 126: 1066-1069.
- Johnson, K. G.; Gideon, R. A.; Loftsgaarden, D. O. (1990) Montana Air Pollution Study: children's health effects. *J. Off. Stat.* 5: 391-407.
- Jollis, J. G.; Ancukiewicz, M.; DeLong, E. R.; Pryor, D. B.; Muhlbaier, L. H.; Mark, D. B. (1993) Discordance of databases designed for claims payment versus clinical information systems: implications for outcomes research. *Ann. Intern. Med.* 119: 844-850.
- Kalkstein, L. S. (1991) A new approach to evaluate the impact of climate on human mortality. *Environ. Health Perspect.* 96: 145-150.
- Kalkstein, L. S. (1993a) Direct impacts in cities. *Lancet* 342: 1397-1399.
- Kalkstein, L. S. (1993b) Climate change and human health. U.S. Environmental Protection Agency; cooperative agreement no. CR-817693.
- Kalkstein, L. S.; Tan, G.; Skindlov, J. (1987) An evaluation of objective clustering procedures for use in synoptic climatological classification. *J. Climate Appl. Meteorol.* 26: 717-730.
- Kalkstein, L. S.; Barthel, C. D.; Ye, H.; Smoyer, K.; Cheng, S.; Greene, J. S.; Nichols, M. C. (1994) The differential impacts of weather and pollution on human mortality. Newark, DE: University of Delaware, Department of Geography, Center for Climatic Research; November.
- Kalkstein, L. S.; Barthel, C. D.; Ye, H.; Smoyer, K.; Cheng, S.; Greene, J. S.; Nichols, M. C. (1995) The impacts of weather and pollution on human mortality. Washington, DC: U.S. Environmental Protection Agency, Office of Policy, Planning, and Evaluation, Climate Change Division; March; cooperative agreement no. CR-817693.
- Katsouyanni, K. (1995) PM mortality review. Report to U.S. Environmental Protection Agency, National Center for Environmental Assessment, Research Triangle Park, NC.
- Katsouyanni, K.; Karakatsani, A.; Messari, I.; Touloumi, G.; Hatzakis, A.; Kalandidi, A.; Trichopoulos, D. (1990a) Air pollution and cause specific mortality in Athens. *J. Epidemiol. Commun. Health* 44: 321-324.

- Katsouyanni, K.; Hatzakis, A.; Kalandidi, A.; Trichopoulos, D. (1990b) Short-term effects of atmospheric pollution on mortality in Athens. *Arch. Hellen. Med.* 7: 126-132.
- Katsouyanni, K.; Trichopoulos, D.; Kalandidi, A.; Tomos, P.; Riboli, E. (1991) A case-control study of air pollution and tobacco smoking in lung cancer among women in Athens. *Prev. Med.* 20: 271-278.
- Katsouyanni, K.; Pantazopoulou, A.; Touloumi, G.; Tselepidaki, I.; Moustris, K.; Asimakopulos, D.; Pouloupoulou, G.; Trichopoulos, D. (1993) Evidence for interaction between air pollution and high temperature in the causation of excess mortality. *Arch. Environ. Health* 48: 235-242.
- Kenline, P. A. (1962) In quest of clean air for Berlin, New Hampshire. Cincinnati, OH: U.S. Department of Health, Education, and Welfare, Public Health Service; technical report no. SEC TR A62-9.
- Kim, Y. S. (1985) Air pollution, climate, socioeconomic status and total mortality in the United States. *Sci. Total Environ.* 42: 245-256.
- Kinney, P. L.; Özkaynak, H. (1991) Associations of daily mortality and air pollution in Los Angeles County. *Environ. Res.* 54: 99-120.
- Kinney, P. L.; Ito, K.; Thurston, G. D. (1995) A sensitivity analysis of mortality/PM<sub>10</sub> associations in Los Angeles. In: Phalen, R. F.; Bates, D. V., eds. *Proceedings of the colloquium on particulate air pollution and human mortality and morbidity*; January 1994; Irvine, CA. *Inhalation Toxicol.* 7: 59-69.
- Kitagawa, T. (1984) Cause analysis of the Yokkaichi asthma episode in Japan. *J. Air Pollut. Control Assoc.* 34: 743-746.
- Klepper, S.; Kamlet, M. S.; Frank, R. G. (1993) Regressor diagnostics for the errors-in-variables model—an application to the health effects of pollution. *J. Environ. Econ. Manage.* 24: 190-211.
- Klerman, L. V. (1988) School absence—a health perspective. *Pediatr. Clin. N. Am.* 35: 1253-1269.
- Koenig, J. Q.; Pierson, W. E.; Horike, M. (1983) The effects of inhaled sulfuric acid on pulmonary function in adolescent asthmatics. *Am. Rev. Respir. Dis.* 128: 221-225.
- Koenig, J. Q.; Larson, T. V.; Hanley, Q. S.; Rebolledo, V.; Dumler, K.; Checkoway, H.; Wang, S.-Z.; Lin, D.; Pierson, W. E. (1993) Pulmonary function changes in children associated with fine particulate matter. *Environ. Res.* 63: 26-38.
- Kornguth, M. L. (1990) School illnesses: who's absent and why? *Pediatr. Nurs.* 16: 95-99.
- Krzyżanowski, M.; Wojtyniak, B. (1982) Ten-year mortality in a sample of an adult population in relation to air pollution. *J. Epidemiol. Commun. Health* 36: 262-268.
- Kunst, A. E.; Looman, C. W. N.; Mackenbach, J. P. (1993) Outdoor air temperature and mortality in the Netherlands: a time-series analysis. *Am. J. Epidemiol.* 137: 331-341.
- Lamm, S. H.; Hall, T. A.; Engel, A.; Rueter, F. H.; White, L. D. (1994) PM<sub>10</sub> particulates: are they the major determinant of pediatric respiratory admissions in Utah County, Utah (1985-1989). In: Dodgson, J.; McCallum, R. I., eds. *Inhaled particles VII: proceedings of an international symposium*; September 1991; Edinburgh, United Kingdom. *Ann. Occup. Hyg.* 38(suppl. 1): 969-972.
- Lave, L. B.; Seskin, E. P. (1970) Air pollution and human health: the quantitative effect, with an estimate of the dollar benefit of pollution abatement, is considered. *Science (Washington, DC)* 169: 723-733.
- Lave, L. B.; Seskin, E. P. (1972) Air pollution, climate, and home heating: their effects on U.S. mortality rates. *Am. J. Public Health* 62: 909-916.

- Lave, L. B.; Seskin, E. P. (1977) Air pollution and human health. Baltimore, MD: The Johns Hopkins University Press.
- Lawther, P. J.; Waller, R. E.; Henderson, M. (1970) Air pollution and exacerbations of bronchitis. *Thorax* 25: 525-539.
- Leamer, E. E. (1978) Specification searches: ad hoc inference with nonexperimental data. New York, NY: John Wiley & Sons. (Bradley, R. A.; Hunter, J. S.; Kendall, D. G.; Watson, G. S., eds. Wiley series in probability and mathematical statistics).
- Lebowitz, M. D.; O'Rourke, M. K.; Dodge, R.; Holberg, C. J.; Corman, G.; Hoshaw, R. W.; Pinnas, J. L.; Barbee, R. A.; Sneller, M. R. (1982) The adverse health effects of biological aerosols, other aerosols, and indoor microclimate on asthmatics and nonasthmatics. *Environ. Int.* 8: 375-380.
- Lebowitz, M. D.; Quackenboss, J. J.; Krzyzanowski, M.; O'Rourke, M. K.; Hayes, C. (1992) Multipollutant exposures and health responses to particulate matter. *Arch. Environ. Health* 47: 71-75.
- Leviton, A.; Bellinger, D.; Allred, E. N.; Rabinowitz, M.; Needleman, H.; Schoenbaum, S. (1993) Pre- and postnatal low-level lead exposure and children's dysfunction in school. *Environ. Res.* 60: 30-43.
- Li, Y.; Roth, H. D. (1995) Daily mortality analysis by using different regression models in Philadelphia County, 1973-1990. In: Phalen, R. F.; Bates, D. V., eds. Proceedings of the colloquium on particulate air pollution and human mortality and morbidity; January 1994; Irvine, CA. *Inhalation Toxicol.* 7: 45-58.
- Liang, K.-Y.; Zeger, S. L. (1986) Longitudinal data analysis using generalized linear models. *Biometrika* 73: 13-22.
- Lindley, D. V. (1947) Regression lines and the linear functional relationship. *J. R. Stat. Soc. B*: 218-224.
- Lioy, P. J.; Vollmuth, T. A.; Lippmann, M. (1985) Persistence of peak flow decrement in children following ozone exposures exceeding the national ambient air quality standard. *J. Air Pollut. Control Assoc.* 35: 1068-1071.
- Lioy, P. J.; Spektor, D.; Thurston, G.; Citak, K.; Lippmann, M.; Bock, N.; Speizer, F. E.; Hayes, C. (1987) The design considerations for ozone and acid aerosol exposure and health investigations: the Fairview Lake summer camp—photochemical smog case study. *Environ. Int.* 13: 271-283.
- Lipfert, F. W. (1978) The association of human mortality with air pollution: statistical analyses by region, by age, and by cause of death. Mantua, NJ: Eureka Publications.
- Lipfert, F. W. (1980a) Differential mortality and the environment: the challenge of multicollinearity in cross-sectional studies. *Energy Sys. Policy* 3: 367-400.
- Lipfert, F. W. (1980b) Sulfur oxides, particulates, and human mortality: synopsis of statistical correlations. *J. Air Pollut. Control Assoc.* 30: 366-371.
- Lipfert, F. W. (1984) Air pollution and mortality: specification searches using SMSA-based data. *J. Environ. Econ. Manage.* 11: 208-243.
- Lipfert, F. W. (1985) Mortality and air pollution: is there a meaningful connection? *Environ. Sci. Technol.* 19: 764-770.
- Lipfert, F. W. (1988) Exposure to acidic sulfates in the atmosphere: review and assessment. Final report. Palo Alto, CA: Electric Power Research Institute; report no. EPRI EA-6150.
- Lipfert, F. W. (1992) An assessment of acid fog. Upton, NY: Brookhaven National Laboratory; report no. BNL-48499.
- Lipfert, F. W. (1993a) Community air pollution and mortality: analysis of 1980 data from US metropolitan areas. I. Particulate air pollution. Upton, NY: U.S. Department of Energy, Brookhaven National Laboratory; report no. BNL 48446-R.

- Lipfert, F. W. (1994a) Air pollution and community health: a critical review and data sourcebook. New York, NY: Van Nostrand Reinhold.
- Lipfert, F. W. (1994b) Filter artifacts associated with particulate measurements: recent evidence and effects on statistical relationships. *Atmos. Environ.* 28: 3233-3249.
- Lipfert, F. W. (1995) Estimating air pollution-mortality risks from cross-sectional studies: prospective vs. ecologic study designs. In: *Particulate matter: health and regulatory issues: proceedings of an international specialty conference; April; Pittsburgh, PA.* Pittsburgh, PA: Air & Waste Management Association; pp. 78-102. (A&WMA publication VIP-49).
- Lipfert, F. W.; Hammerstrom, T. (1992) Temporal patterns in air pollution and hospital admissions. *Environ. Res.* 59: 374-399.
- Lipfert, F. W.; Morris, S. C. (1991) Air pollution benefit-cost assessment. *Science (Washington, DC)* 253: 606.
- Lipfert, F. W.; Wyzga, R. E. (1995a) Uncertainties in identifying responsible pollutants in observational epidemiology studies. In: Phalen, R. F.; Bates, D. V., eds. *Proceedings of the colloquium on particulate air pollution and human mortality and morbidity, part II; January 1994; Irvine, CA.* *Inhalation Toxicol.* 7: 671-689.
- Lipfert, F. W.; Wyzga, R. E. (1995b) Air pollution and mortality: issues and uncertainties. *J. Air Waste Manage. Assoc.* 45: 949-966.
- Lipfert, F. W.; Malone, R. G.; Daum, M. L.; Mendell, N. R.; Yang, C.-C. (1988) A statistical study of the macroepidemiology of air pollution and total mortality. Upton, NY: U.S. Department of Energy, Brookhaven National Laboratory; report no. BNL-52122.
- Lippmann, M. (1985) Airborne acidity: estimates of exposure and human health effects. *Environ. Health Perspect.* 63: 63-70.
- Lippmann, M.; Ito, K. (1995) Separating the effects of temperature and season on daily mortality from those of air pollution in London: 1965-1972. In: Phalen, R. F.; Bates, D. V., eds. *Proceedings of the colloquium on particulate air pollution and human mortality and morbidity; January 1994; Irvine, CA.* *Inhalation Toxicol.* 7: 85-97.
- Lippmann, M.; Thurston, G. (1996) Sulfate concentrations as an indicator of ambient particulate matter air pollution for health risk calculations. *J. Exposure Anal. Environ. Epidemiol.*: accepted.
- Lippmann, M.; Liou, P. J.; Leikauf, G.; Green, K. B.; Baxter, D.; Morandi, M.; Pasternack, B. S.; Fife, D.; Speizer, F. E. (1983) Effects of ozone on the pulmonary function of children. In: Lee, S. D.; Mustafa, M. G.; Mehlman, M. A., eds. *International symposium on the biomedical effects of ozone and related photochemical oxidants; March 1982; Pinehurst, NC.* Princeton, NJ: Princeton Scientific Publishers, Inc.; pp. 423-446. (*Advances in modern environmental toxicology*: v. 5).
- Lunn, J. E.; Knowelden, J.; Handyside, A. J. (1967) Patterns of respiratory illness in Sheffield infant schoolchildren. *Br. J. Prev. Soc. Med.* 21: 7-16.
- Lunn, J. E.; Knowelden, J.; Roe, J. W. (1970) Patterns of respiratory illness in Sheffield junior schoolchildren: a follow-up study. *Br. J. Prev. Soc. Med.* 24: 223-228.
- Lyon, J. L.; Mori, M.; Gao, R. (1995) Is there a causal association between excess mortality and exposure to PM-10 air pollution? Additional analyses by location, year, season and cause of death. In: Phalen, R. F.; Bates, D. V., eds. *Proceedings of the colloquium on particulate air pollution and human mortality and morbidity, part II; January 1994; Irvine, CA.* *Inhalation Toxicol.* 7: 603-614.

- Mackenbach, J. P.; Looman, C. W. N.; Kunst, A. E. (1993) Air pollution, lagged effects of temperature, and mortality: The Netherlands 1979-87. *J. Epidemiol. Commun. Health* 47: 121-126.
- Martin, A. E. (1964) Mortality and morbidity statistics and air pollution. *Proc. R. Soc. Med.* 57: 969-975.
- Martin, A. E.; Bradley, W. H. (1960) Mortality, fog and atmospheric pollution: an investigation during the winter of 1958-59. *Mon. Bull. Minist. Health Public Health Lab. Serv. (GB)* 19: 56-73.
- Martinez, F. D.; Morgan, W. J.; Wright, A. L.; Holberg, C. J.; Taussig, L. M. (1988) Diminished lung function as a predisposing factor for wheezing respiratory illness in infants. *N. Engl. J. Med.* 319: 1112-1117.
- Martinez, F. D.; Taussig, L. M.; Morgan, W. J. (1990) Infants with upper respiratory illnesses have significant reductions in maximal expiratory flow. *Pediatr. Pulmonol.* 9: 91-95.
- Martinez, F. D.; Morgan, W. J.; Wright, A. L.; Holberg, C.; Taussig, L. M.; Group Health Medical Associates. (1991) Initial airway function is a risk factor for recurrent wheezing respiratory illnesses during the first three years of life. *Am. Rev. Respir. Dis.* 143: 312-316.
- Martinez, F. D.; Wright, A. L.; Taussig, L. M.; Holberg, C. J.; Halonen, M.; Morgan, W. J.; Group Health Medical Associates. (1995) Asthma and wheezing in the first six years of life. *N. Engl. J. Med.* 332: 133-138.
- Mazumdar, S.; Sussman, N. (1983) Relationships of air pollution to health: results from the Pittsburgh study. *Arch. Environ. Health* 38: 17-24.
- Mazumdar, S.; Schimmel, H.; Higgins, I. (1981) Daily mortality, smoke and SO<sub>2</sub> in London, England 1959 to 1972. In: Frederick, E. R., ed. *A specialty conference on: the proposed SO<sub>x</sub> and particulate standard; September 1980; Atlanta, GA. Pittsburgh, PA: Air Pollution Control Association; pp. 219-239.*
- Mazumdar, S.; Schimmel, H.; Higgins, I. T. T. (1982) Relation of daily mortality to air pollution: an analysis of 14 London winters, 1958/59-1971/72. *Arch. Environ. Health* 37: 213-220.
- McConnochie, K. M.; Hall, C. B.; Barker, W. H. (1988) Lower respiratory tract illness in the first two years of life: epidemiologic patterns and costs in a suburban pediatric practice. *Am. J. Public Health* 78: 34-39.
- McCullagh, P.; Nelder, J. A. (1983) *Generalized linear models*. New York, NY: Chapman and Hall. (Monographs on statistics and applied probability).
- McCullagh, P.; Nelder, J. A. (1989) *Generalized linear models*. 2nd ed. London, United Kingdom: Chapman and Hall.
- McPherson, K.; Wennberg, J. E.; Hovind, O. B.; Clifford, P. (1982) Small-area variations in the use of common surgical procedures: an international comparison of New England, England, and Norway. *N. Engl. J. Med.* 307: 1310-1314.
- Mendelsohn, R.; Orcutt, G. (1979) An empirical analysis of air pollution dose-response curves. *J. Environ. Econ. Manage.* 6: 85-106.
- Mickey, R. M.; Greenland, S. (1989) The impact of confounder selection criteria on effect estimation. *Am. J. Epidemiol.* 129: 125-137, 1066.
- Moolgavkar, S. H. (1994) Air pollution and mortality [letter]. *N. Engl. J. Med.* 330: 1237-1238.
- Moolgavkar, S. H.; Luebeck, E. G.; Hall, T. A.; Anderson, E. L. (1995a) Particulate air pollution, sulfur dioxide, and daily mortality: a reanalysis of the Steubenville data. In: Phalen, R. F.; Bates, D. V., eds. *Proceedings of the colloquium on particulate air pollution and human mortality and morbidity; January 1994; Irvine, CA. Inhalation Toxicol.* 7: 35-44.

- Moolgavkar, S. H.; Luebeck, E. G.; Hall, T. A.; Anderson, E. L. (1995b) Air pollution and daily mortality in Philadelphia. *Epidemiology* 6: 476-484.
- Morris, S. C.; Shapiro, M. A.; Waller, J. H. (1976) Adult mortality in two communities with widely different air pollution levels. *Arch. Environ. Health* 31: 248-254.
- Moshkovitz, Y.; Sclarovsky, S.; Behar, S.; Reicher-Reiss, H.; Kaplinsky, E.; Goldbourt, U.; SPRINT Study Group. (1993) Infarct site-related mortality in patients with recurrent myocardial infarction. *Am. J. Med.* 94: 388-394.
- Murphy, T. F.; Henderson, F. W.; Clyde, W. A., Jr.; Collier, A. M.; Denny, F. W. (1981) Pneumonia: an eleven-year study in a pediatric practice. *Am. J. Epidemiol.* 113: 12-21.
- National Center for Health Statistics. (1993a) Advance report of final mortality statistics, 1991. Hyattsville, MD: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention. (Monthly vital statistics report: v. 42, no. 2, suppl.).
- National Center for Health Statistics. (1993b) National Hospital Discharge Survey: annual summary, 1991. Hyattsville, MD: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention; DHHS publication no. (PHS)93-1775. (Series 13, data from the National Health Survey: no. 114).
- National Center for Health Statistics. (1994a) Mortality surveillance system charts. *Mon. Vital Stat. Rep.* 43(5): 6-7.
- National Center for Health Statistics. (1994b) Detailed diagnoses and procedures, National Hospital Discharge Survey, 1992. Hyattsville, MD: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention; DHHS publication no. (PHS) 94-1779. (Series 13, data from the National Health Survey: no. 118).
- National Center for Health Statistics. (1994c) Current estimates from the National Health Interview Survey, 1992. Hyattsville, MD: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention; DHHS publication no. (PHS) 94-1517. (Data from the National Health Survey: series 10, no. 189).
- National Institutes of Health. (1991) Guidelines for the diagnosis and management of asthma. Bethesda, MD: U.S. Department of Health and Human Services, National Heart, Lung, and Blood Institute, National Asthma Education Program; publication no. 91-3042.
- Neas, L. M.; Dockery, D. W.; Ware, J. H.; Spengler, J. D.; Ferris, B. G., Jr.; Speizer, F. E. (1994) Concentration of indoor particulate matter as a determinant of respiratory health in children. *Am. J. Epidemiol.* 139: 1088-1099.
- Neas, L. M.; Dockery, D. W.; Koutrakis, P.; Tollerud, D. J.; Speizer, F. E. (1995) The association of ambient air pollution with twice daily peak expiratory flow rate measurements in children. *Am. J. Epidemiol.* 141: 111-122.
- Örtqvist, Å.; Hedlund, J.; Grillner, L.; Jalonen, E.; Kallings, I.; Leinonen, M.; Kalin, M. (1990) Aetiology, outcome and prognostic factors in community-acquired pneumonia requiring hospitalization. *Eur. Respir. J.* 3: 1105-1113.
- Osborne, M. L.; Vollmer, W. M.; Buist, A. S. (1992) Diagnostic accuracy of asthma within a health maintenance organization. *J. Clin. Epidemiol.* 45: 403-411.
- Ostro, B. D. (1983) The effects of air pollution on work loss and morbidity. *J. Environ. Econ. Manage.* 10: 371-382.
- Ostro, B. (1984) A search for a threshold in the relationship of air pollution to mortality: a reanalysis of data on London winters. *Environ. Health Perspect.* 58: 397-399.
- Ostro, B. D. (1987) Air pollution and morbidity revisited: a specification test. *J. Environ. Econ. Manage.* 14: 87-98.

- Ostro, B. (1993) The association of air pollution and mortality: examining the case for inference. *Arch. Environ. Health* 48: 336-342.
- Ostro, B. D.; Rothschild, S. (1989) Air pollution and acute respiratory morbidity: an observational study of multiple pollutants. *Environ. Res.* 50: 238-247.
- Ostro, B.; Lipsett, M.; Wiener, M.; Selner, J. C. (1989) A panel study of the effect of acid aerosols on asthmatics. Presented at: 82nd annual meeting and exhibition of the Air and Waste Management Association; June; Anaheim, CA. Pittsburgh, PA: Air & Waste Management Association; paper no. 89-94.1.
- Ostro, B. D.; Lipsett, M. J.; Wiener, M. B.; Selner, J. C. (1991) Asthmatic responses to airborne acid aerosols. *Am. J. Public Health* 81: 694-702.
- Ostro, B. D.; Lipsett, M. J.; Mann, J. K.; Krupnick, A.; Harrington, W. (1993) Air pollution and respiratory morbidity among adults in Southern California. *Am. J. Epidemiol.* 137: 691-700.
- Ostro, B. D.; Lipsett, M. J.; Mann, J. K.; Braxton-Owens, H.; White, M. C. (1995) Air pollution and asthma exacerbations among African-American children in Los Angeles. In: Phalen, R. F.; Bates, D. V., eds. *Proceedings of the colloquium on particulate air pollution and human mortality and morbidity, part II*; January 1994; Irvine, CA. *Inhalation Toxicol.* 7: 711-722.
- Ostro, B.; Sanchez, J. M.; Aranda, C.; Eskeland, G. S. (1996) Air pollution and mortality: results from a study of Santiago, Chile. In: Lippmann, M., ed. *Papers from the ISEA-ISEE annual meeting*; September 1994; Research Triangle Park, NC. *J. Exposure Anal. Environ. Epidemiol.*: in press.
- Özkaynak, H.; Spengler, J. D. (1985) Analysis of health effects resulting from population exposures to acid precipitation precursors. *Environ. Health Perspect.* 63: 45-55.
- Özkaynak, H.; Thurston, G. D. (1987) Associations between 1980 U.S. mortality rates and alternative measures of airborne particle concentration. *Risk Anal.* 7: 449-461.
- Özkaynak, H.; Spengler, J. D.; Garsd, A.; Thurston, G. D. (1986) Assessment of population health risks resulting from exposures to airborne particles. In: Lee, S. D.; Schneider, T.; Grant, L. D.; Verkerk, P. J., eds. *Aerosols: research, risk assessment and control strategies, proceedings of the second U.S.-Dutch international symposium*; May 1985; Williamsburg, VA. Chelsea, MI: Lewis Publishers, Inc.; pp. 1067-1080.
- Özkaynak, H.; Xue, J.; Severance, P.; Burnett, R.; Raizenne, M. (1994) Associations between daily mortality, ozone, and particulate air pollution in Toronto, Canada. Presented at: *Colloquium on particulate air pollution and human mortality and morbidity: program and abstracts*; January; Irvine, CA. Irvine, CA: University of California Irvine, Air Pollution Health Effects Laboratory; p. P1.13; report no. 94-02.
- Parcel, G. S.; Gilman, S. C.; Nader, P. R.; Bunce, H. (1979) A comparison of absentee rates of elementary schoolchildren with asthma and nonasthmatic schoolmates. *Pediatrics* 64: 878-881.
- Perry, G. B.; Chai, H.; Dickey, D. W.; Jones, R. H.; Kinsman, R. A.; Morrill, C. G.; Spector, S. L.; Weiser, P. C. (1983) Effects of particulate air pollution on asthmatics. *Am. J. Public Health* 73: 50-56.
- Pocock, S. J.; Shaper, A. G.; Cook, D. G.; Packham, R. F.; Lacey, R. F.; Powell, P.; Russell, P. F. (1980) British regional heart study: geographic variations in cardiovascular mortality, and the role of water quality. *Br. Med. J.* 280: 1243-1249.
- Pönkä, A. (1991) Asthma and low level air pollution in Helsinki. *Arch. Environ. Health* 46: 262-270.
- Pönkä, A.; Virtanen, M. (1994) Chronic bronchitis, emphysema, and low-level air pollution in Helsinki, 1987-1989. *Environ. Res.* 65: 207-217.

- Pope, C. A., III. (1989) Respiratory disease associated with community air pollution and a steel mill, Utah Valley. *Am. J. Public Health* 79: 623-628.
- Pope, C. A., III. (1991) Respiratory hospital admissions associated with PM<sub>10</sub> pollution in Utah, Salt Lake, and Cache Valleys. *Arch. Environ. Health* 46: 90-97.
- Pope, C. A., III. (1994) Particulate pollution and mortality in Utah valley. Prepared for: Critical evaluation workshop on particulate matter—mortality epidemiology studies; November; Raleigh, NC. Provo, UT: Brigham Young University.
- Pope, C. A., III; Dockery, D. W. (1992) Acute health effects of PM<sub>10</sub> pollution on symptomatic and asymptomatic children. *Am. Rev. Respir. Dis.* 145: 1123-1128.
- Pope, C. A., III; Kalkstein, L. S. (1996) Synoptic weather modeling and estimates of the exposure-response relationship between daily mortality and particulate air pollution. *Environ. Health Perspect.* 104: in press.
- Pope, C. A., III; Kanner, R. E. (1993) Acute effects of PM<sub>10</sub> pollution on pulmonary function of smokers with mild to moderate chronic obstructive pulmonary disease. *Am. Rev. Respir. Dis.* 147: 1336-1340.
- Pope, C. A., III; Dockery, D. W.; Spengler, J. D.; Raizenne, M. E. (1991) Respiratory health and PM<sub>10</sub> pollution: a daily time series analysis. *Am. Rev. Respir. Dis.* 144: 668-674.
- Pope, C. A., III; Schwartz, J.; Ransom, M. R. (1992) Daily mortality and PM<sub>10</sub> pollution in Utah valley. *Arch. Environ. Health* 47: 211-217.
- Pope, C. A., III; Dockery, D. W.; Schwartz, J. (1995a) Review of epidemiological evidence of health effects of particulate air pollution. In: Phalen, R. F.; Bates, D. V., eds. *Proceedings of the colloquium on particulate air pollution and human mortality and morbidity*; January 1994; Irvine, CA. *Inhalation Toxicol.* 7: 1-18.
- Pope, C. A., III; Thun, M. J.; Namboodiri, M. M.; Dockery, D. W.; Evans, J. S.; Speizer, F. E.; Heath, C. W., Jr. (1995b) Particulate air pollution as a predictor of mortality in a prospective study of U.S. adults. *Am. J. Respir. Crit. Care Med.* 151: 669-674.
- Quackenboss, J. J.; Krzyzanowski, M.; Lebowitz, M. D. (1991) Exposure assessment approaches to evaluate respiratory health effects of particulate matter and nitrogen dioxide. *J. Exposure Anal. Environ. Epidemiol.* 1: 83-107.
- Quandt, R. E. (1958) The estimation of the parameters of a linear regression system obeying two separate regimes. *J. Am. Stat. Assoc.* 53: 873-880.
- Queiros, M.; Bonito-Vitor, A.; Costa-Pereira, A.; Costa Maia, J. (1990) Childhood asthma and outdoor air pollution in Oporto area. *Allergol. Immunopathol.* 18: 291-295.
- Raizenne, M.; Burnett, R.; Stern, B.; Meranger, J. C. (1987) Transported air pollutants and respiratory health in two Canadian communities. *Chest* 91: 314.
- Raizenne, M. E.; Burnett, R. T.; Stern, B.; Franklin, C. A.; Spengler, J. D. (1989) Acute lung function responses to ambient acid aerosol exposures in children. *Environ. Health Perspect.* 79: 179-185.
- Raizenne, M.; Neas, L. M.; Damokosh, A. I.; Dockery, D. W.; Spengler, J. D.; Koutrakis, P.; Ware, J. H.; Speizer, F. E. (1996) Health effects of acid aerosols on North American children: pulmonary function. *Environ. Health Perspect.*: accepted.
- Ramlow, J. M.; Kuller, L. H. (1990) Effects of the summer heat wave of 1988 on daily mortality in Allegheny County, PA. *Public Health Rep.* 105: 283-289.

- Ransom, M. R.; Pope, C. A., III. (1992) Elementary school absences and PM<sub>10</sub> pollution in Utah Valley. *Environ. Res.* 58: 204-219.
- Ricci, P. F.; Wyzga, R. E. (1983) An overview of cross-sectional studies of mortality and air pollution and related statistical issues. *Environ. Int.* 9: 177-194.
- Richardson, S. L.; Renz, K. K.; Vogel, T. T.; Graham, J. E., Jr.; Kaufman, J. (1991) Small area analysis shows differences in utilization. *Qual. Assur. Util. Rev.* 6: 91-94.
- Rieves, R. D.; Bass, D.; Carter, R. R.; Griffith, J. E.; Norman, J. R. (1993) Severe COPD and acute respiratory failure: correlates for survival at the time of tracheal intubation. *Chest* 104: 854-860.
- Robertson, J. M.; Ingalls, T. H. (1989) A case-control study of circulatory, malignant, and respiratory morbidity in carbon black workers in the United States. *Am. Ind. Hyg. Assoc. J.* 50: 510-515.
- Roemer, W.; Hoek, G.; Brunekreef, B. (1993) Effect of ambient winter air pollution on respiratory health of children with chronic respiratory symptoms. *Am. Rev. Respir. Dis.* 147: 118-124.
- Rogot, E.; Sorlie, P. D.; Johnson, N. J.; Schmitt, C. (1992) A mortality study of 1.3 million persons by demographic, social, and economic factors: 1979-1985 follow-up. Bethesda, MD: National Institutes of Health; NIH publication no. 92-3297.
- Rothman, K. J. (1986) *Modern epidemiology*. Boston, MA: Little, Brown and Co.
- Rothman, N.; Ford, D. P.; Baser, M. E.; Hansen, J. A.; O'Toole, T.; Tockman, M. S.; Strickland, P. T. (1991) Pulmonary function and respiratory symptoms in wildland firefighters. *J. Occup. Med.* 33: 1163-1167.
- Saldiva, P. H. N.; Lichtenfels, A. J. F. C.; Paiva, P. S. O.; Barone, I. A.; Martins, M. A.; Massad, E.; Pereira, J. C. R.; Xavier, V. P.; Singer, J. M.; Böhm, G. M. (1994) Association between air pollution and mortality due to respiratory diseases in children in São Paulo, Brazil: a preliminary report. *Environ. Res.* 65: 218-225.
- Saldiva, P. H. N.; Pope, C. A., III; Schwartz, J.; Dockery, D. W.; Lichtenfels, A. J.; Salge, J. M.; Barone, I.; Böhm, G. M. (1995) Air pollution and mortality in elderly people: a time-series study in São Paulo, Brazil. *Arch. Environ. Health* 50: 159-163.
- Samet, J. M.; Utell, M. J. (1990) The risk of nitrogen dioxide: what have we learned from epidemiological and clinical studies? *Toxicol. Ind. Health* 6: 247-262.
- Samet, J. M.; Tager, I. B.; Speizer, F. E. (1983) The relationship between respiratory illness in childhood and chronic air-flow obstruction in adulthood. *Am. Rev. Respir. Dis.* 127: 508-523.
- Samet, J. M.; Zeger, S. L.; Berhane, K. (1995) The association of mortality and particulate air pollution. In: *Particulate air pollution and daily mortality: replication and validation of selected studies, the phase I report of the particle epidemiology evaluation project* [preprint]. Cambridge, MA: Health Effects Institute; pp. 1-104.
- Samet, J. M.; Zeger, S. L.; Kelsall, J. E.; Xu, J. (1996a) Air pollution and mortality in Philadelphia, 1974-1988, report to the Health Effects Institute on phase IB: Particle Epidemiology Evaluation Project. Cambridge, MA: Health Effects Institute; accepted.
- Samet, J. M.; Zeger, S. L.; Kelsall, J. E.; Xu, J.; Kalkstein, L. S. (1996b) Weather, air pollution and mortality in Philadelphia, 1973-1980, report to the Health Effects Institute on phase IB, Particle Epidemiology Evaluation Project. Cambridge, MA: Health Effects Institute; review draft.
- Sandvik, L.; Erikssen, J.; Thaulow, E.; Erikssen, G.; Mundal, R.; Rodahl, K. (1993) Physical fitness as a predictor of mortality among healthy, middle-aged Norwegian men. *N. Engl. J. Med.* 328: 533-537.

- Schenker, M. B.; Speizer, F. E.; Samet, J. M.; Gruhl, J.; Batterman, S. (1983) Health effects of air pollution due to coal combustion in the Chestnut Ridge region of Pennsylvania: results of cross-sectional analysis in adults. *Arch. Environ. Health* 38: 325-330.
- Schimmel, H. (1978) Evidence for possible acute health effects of ambient air pollution from time series analysis: methodological questions and some new results based on New York City daily mortality, 1963-1976. *Bull. N. Y. Acad. Med.* 54: 1052-1108.
- Schrenk, H. H.; Heimann, H.; Clayton, G. D.; Gafafer, W. M.; Wexler, H. (1949) Air pollution in Donora, PA. Epidemiology of the unusual smog episode of October 1948: preliminary report. Washington, DC: Public Health Service; Public Health Service bulletin no. 306.
- Schwartz, J. (1989) Lung function and chronic exposure to air pollution: a cross-sectional analysis of NHANES II. *Environ. Res.* 50: 309-321.
- Schwartz, J. (1991a) Particulate air pollution and daily mortality in Detroit. *Environ. Res.* 56: 204-213.
- Schwartz, J. (1991b) The first author replies [letter re Fleisher and Nayeri (1991)]. *Am. J. Epidemiol.* 133: 632-633.
- Schwartz, J. (1992) Particulate air pollution and daily mortality: a synthesis. *Public Health Rev.* 19: 39-60.
- Schwartz, J. (1993a) Air pollution and daily mortality in Birmingham, Alabama. *Am. J. Epidemiol.* 137: 1136-1147.
- Schwartz, J. (1993b) Particulate air pollution and chronic respiratory disease. *Environ. Res.* 62: 7-13.
- Schwartz, J. (1994a) Total suspended particulate matter and daily mortality in Cincinnati, Ohio. *Environ. Health Perspect.* 102: 186-189.
- Schwartz, J. (1994b) Air pollution and daily mortality: a review and meta analysis. *Environ. Res.* 64: 36-52.
- Schwartz, J. (1994c) What are people dying of on high air pollution days? *Environ. Res.* 64: 26-35.
- Schwartz, J. (1994d) Air pollution and hospital admissions for the elderly in Detroit, Michigan. *Am. J. Respir. Crit. Care Med.* 150: 648-655.
- Schwartz, J. (1994e) Air pollution and hospital admissions for the elderly in Birmingham, Alabama. *Am. J. Epidemiol.* 139: 589-598.
- Schwartz, J. (1994f) PM<sub>10</sub>, ozone, and hospital admissions for the elderly in Minneapolis, MN. *Arch. Environ. Health* 49: 366-374.
- Schwartz, J. (1994g) Nonparametric smoothing in the analysis of air pollution and respiratory illness. *Can. J. Stat.* 22: 1-17.
- Schwartz, J. (1994h) The use of generalized additive models in epidemiology. In: IBC'94, XVIIth International Biometric Society conference proceedings, volume 1: invited papers; August; Hamilton, Ontario, Canada. Hamilton, Ontario, Canada: McMaster University, Department of Mathematics and Statistics, IBC'94 Local Organizing Committee; pp. 55-80.
- Schwartz, J. (1995a) Short term fluctuations in air pollution and hospital admissions of the elderly for respiratory disease. *Thorax* 50: 531-538.
- Schwartz, J. (1995b) Health effects of air pollution from traffic: ozone and particulate matter. In: Fletcher, T., ed. *Health at the crossroads: transportation policy and urban health, proceedings of the fifth annual public health forum of*

the London School of Hygiene and Tropical Medicine; April; London, United Kingdom. New York, NY: John Wiley & Sons, Inc.; in preparation.

- Schwartz, J. (1996) Air pollution and hospital admissions for respiratory disease. *Epidemiology* 7: 20-28.
- Schwartz, J.; Dockery, D. W. (1992a) Increased mortality in Philadelphia associated with daily air pollution concentrations. *Am. Rev. Respir. Dis.* 145: 600-604.
- Schwartz, J.; Dockery, D. W. (1992b) Particulate air pollution and daily mortality in Steubenville, Ohio. *Am. J. Epidemiol.* 135: 12-19.
- Schwartz, J.; Marcus, A. H. (1986) Statistical reanalyses of data relating mortality to air pollution during London winters 1958-1972. Washington, DC: U.S. Environmental Protection Agency, Office of Policy, Planning and Evaluation.
- Schwartz, J.; Marcus, A. (1990) Mortality and air pollution in London: a time series analysis. *Am. J. Epidemiol.* 131: 185-194.
- Schwartz, J.; Morris, R. (1995) Air pollution and hospital admissions for cardiovascular disease in Detroit, Michigan. *Am. J. Epidemiol.* 142: 23-35.
- Schwartz, J.; Spix, C.; Wichmann, H. E.; Malin, E. (1991a) Air pollution and acute respiratory illness in five German communities. *Environ. Res.* 56: 1-14.
- Schwartz, J.; Wypij, D.; Dockery, D.; Ware, J.; Zeger, S.; Spengler, J.; Ferris, B., Jr. (1991b) Daily diaries of respiratory symptoms and air pollution: methodological issues and results. *Environ. Health Perspect.* 90: 181-187.
- Schwartz, J.; Slater, D.; Larson, T. V.; Pierson, W. E.; Koenig, J. Q. (1993) Particulate air pollution and hospital emergency room visits for asthma in Seattle. *Am. Rev. Respir. Dis.* 147: 826-831.
- Schwartz, J.; Dockery, D. W.; Neas, L. M.; Wypij, D.; Ware, J. H.; Spengler, J. D.; Koutrakis, P.; Speizer, F. E.; Ferris, B. G., Jr. (1994) Acute effects of summer air pollution on respiratory symptom reporting in children. *Am. J. Respir. Crit. Care Med.* 150: 1234-1242.
- Schwartz, J.; Dockery, D. W.; Neas, L. M. (1996a) Is daily mortality associated specifically with fine particles? *J. Air Waste Manage. Assoc.*: accepted.
- Schwartz, J.; Spix, C.; Touloumi, G.; Bacharova, L.; Barumamdzadeh, T.; Le Tertre, A.; Piekarksi, T.; Ponce de Leon, A.; Ponka, A.; Rossi, G.; Saez, M.; Shouten, J. P. (1996b) Methodological issues in studies of air pollution and daily counts of deaths or hospital admissions. *J. Epidemiol. Commun. Health*: in press.
- Schwarz, G. (1978) Estimating the dimension of a model. *Ann. Stat.* 6: 461-464.
- Shapiro, S. (1994) Meta-analysis/shmeta-analysis. *Am. J. Epidemiol.* 140: 771-778.
- Shumway, R. H.; Tai, R. Y.; Tai, L. P.; Pawitan, Y. (1983) Statistical analysis of daily London mortality and associated weather and pollution effects. Sacramento, CA: California Air Resources Board; contract no. A1-154-33.
- Shumway, R. H.; Azari, A. S.; Pawitan, Y. (1988) Modeling mortality fluctuations in Los Angeles as functions of pollution and weather effects. *Environ. Res.* 45: 224-241.
- Shusterman, D.; Kaplan, J. Z.; Canabarro, C. (1993) Immediate health effects of an urban wildfire. *West. J. Med.* 158: 133-138.
- Siegel, P. Z.; Frazier, E. L.; Mariolis, P.; Brackbill, R. M.; Smith, C. (1993) Behavioral risk factor surveillance, 1991: monitoring progress toward the nation's year 2000 health objectives. *Morb. Mortal. Wkly Rep.* 42: 1-20.

- Silverman, F.; Hosein, H. R.; Corey, P.; Holton, S.; Tarlo, S. M. (1992) Effects of particulate matter exposure and medication use on asthmatics. *Arch. Environ. Health* 47: 51-56.
- Skobeloff, E. M.; Spivey, W. H.; St. Clair, S. S.; Schoffstall, J. M. (1992) The influence of age and sex on asthma admissions. *JAMA J. Am. Med. Assoc.* 268: 3437-3440.
- Smith, V. K. (1975) Mortality-air pollution relationships: a comment. *JASA J. Am. Stat. Assoc.* 70: 341-343.
- Sorlie, P. D.; Rogot, E. (1990) Mortality by employment status in the National Longitudinal Mortality Study. *Am. J. Epidemiol.* 132: 983-992.
- Speizer, F. E. (1989) Studies of acid aerosols in six cities and in a new multi-city investigation: design issues. *Environ. Health Perspect.* 79: 61-67.
- Spektor, D. M.; Yen, B. M.; Lippmann, M. (1989) Effect of concentration and cumulative exposure of inhaled sulfuric acid on tracheobronchial particle clearance in healthy humans. In: Symposium on the health effects of acid aerosols; October 1987; Research Triangle Park, NC. *Environ. Health Perspect.* 79: 167-172.
- Spektor, D. M.; Lippmann, M.; Liroy, P. J.; Thurston, G. D.; Citak, K.; James, D. J.; Bock, N.; Speizer, F. E.; Hayes, C. (1988) Effects of ambient ozone on respiratory function in active, normal children. *Am. Rev. Respir. Dis.* 137: 313-320.
- Spektor, D. M.; Hofmeister, V. A.; Artaxo, P.; Bague, J. A. P.; Echelar, F.; Nogueira, D. P.; Hayes, C.; Thurston, G. D.; Lippmann, M. (1991) Effects of heavy industrial pollution on respiratory function in the children of Cubatao, Brazil: a preliminary report. *Environ. Health Perspect.* 94: 51-54.
- Spengler, J. D.; Allen, G. A.; Foster, S.; Severance, P.; Ferris, B., Jr. (1986) Sulfuric acid and sulfate aerosol events in two U. S. cities. In: Lee, S. D.; Schneider, T.; Grant, L. D.; Verkerk, P. J., eds. *Aerosols: research, risk assessment and control strategies - proceedings of the second U.S.-Dutch international symposium*; May 1985; Williamsburg, VA. Chelsea, MI: Lewis Publishers, Inc.; pp. 107-120.
- Spengler, J. D.; Keeler, G. J.; Koutrakis, P.; Ryan, P. B.; Raizenne, M.; Franklin, C. A. (1989) Exposures to acidic aerosols. In: Symposium on the health effects of acid aerosols; October 1987; Research Triangle Park, NC. *Environ. Health Perspect.* 79: 43-51.
- Spengler, J. D.; Koutrakis, P.; Dockery, D. W.; Raizenne, M.; Speizer, F. E. (1996) Health effects of acid aerosols on North American children: air pollution exposures. *Environ. Health Perspect.*: in press.
- Spix, C.; Heinrich, J.; Dockery, D.; Schwartz, J.; Völksch, G.; Schwinkowski, K.; Collen, C.; Wichmann, H. E. (1993) Air pollution and daily mortality in Erfurt, East Germany, 1980-1989. *Environ. Health Perspect.* 101: 518-526.
- Spix, C.; Heinrich, J.; Dockery, D.; Schwartz, J.; Völksch, G.; Schwinkowski, K.; Collen, C.; Wichmann, H. E. (1994) Summary of the analysis and reanalysis corresponding to the publication Air pollution and daily mortality in Erfurt, East Germany 1980-1989. Summary report for: Critical evaluation workshop on particulate matter—mortality epidemiology studies; November; Raleigh, NC. Wuppertal, Germany: Bergische Universität-Gesamthochschule Wuppertal.
- Stern, B.; Jones, L.; Raizenne, M.; Burnett, R.; Meranger, J. C.; Franklin, C. A. (1989) Respiratory health effects associated with ambient sulfates and ozone in two rural Canadian communities. *Environ. Res.* 49: 20-39.
- Stern, B. R.; Raizenne, M. E.; Burnett, R. T.; Jones, L.; Kearney, J.; Franklin, C. A. (1994) Air pollution and childhood respiratory health: exposure to sulfate and ozone in 10 Canadian rural communities. *Environ. Res.* 66: 125-142.
- Stokinger, H. E. (1972) Concepts of thresholds in standards setting: an analysis of the concept and its application to industrial air limits (TLVs). *Arch. Environ. Health* 25: 153-157.

- Storr, J.; Lenney, W. (1989) School holidays and admissions with asthma. *Arch. Dis. Child.* 64: 103-107.
- Studnicka, M. J.; Frischer, T.; Meinert, R.; Studnicka-Benke, A.; Hajek, K.; Spengler, J. D.; Neumann, M. G. (1995) Acidic particles and lung function in children: a summer camp study in the Austrian Alps. *Am. J. Respir. Crit. Care Med.* 151: 423-430.
- Styer, P.; McMillan, N.; Gao, F.; Davis, J.; Sacks, J. (1995) The effect of airborne particulate matter on daily death counts. *Environ. Health Perspect.* 103: 490-497.
- Suh, H. H.; Allen, G. A.; Koutrakis, P.; Burton, R. M. (1995) Spatial variation in acidic sulfate and ammonia concentrations within metropolitan Philadelphia. *J. Air Waste Manage. Assoc.* 45: 442-452.
- Sunyer, J.; Antó, J. M.; Murillo, C.; Sáez, M. (1991) Effects of urban air pollution on emergency room admissions for chronic obstructive pulmonary disease. *Am. J. Epidemiol.* 134: 277-286.
- Sunyer, J.; Sáez, M.; Murillo, C.; Castellsague, J.; Martínez, F.; Antó, J. M. (1993) Air pollution and emergency room admissions for chronic obstructive pulmonary disease: a 5-year study. *Am. J. Epidemiol.* 137: 701-705.
- Tager, I. B.; Segal, M. R.; Speizer, F. E.; Weiss, S. T. (1988) The natural history of forced expiratory volumes: effect of cigarette smoking and respiratory symptoms. *Am. Rev. Respir. Dis.* 138: 837-849.
- Tager, I. B.; Hanrahan, J. P.; Tosteson, T. D.; Castile, R. G.; Brown, R. W.; Weiss, S. T.; Speizer, F. E. (1993) Lung function, pre- and post-natal smoke exposure, and wheezing in the first year of life. *Am. Rev. Respir. Dis.* 147: 811-817.
- Tashkin, D. P.; Detels, R.; Simmons, M.; Liu, H.; Coulson, A. H.; Sayre, J.; Rokaw, S. (1994) The UCLA population studies of chronic obstructive respiratory disease: XI. impact of air pollution and smoking on annual change in forced expiratory volume in one second. *Am. J. Respir. Crit. Care Med.* 149: 1209-1217.
- Thibodeau, L. A.; Reed, R. B.; Bishop, Y. M. M.; Kammerman, L. A. (1980) Air pollution and human health: a review and reanalysis. *Environ. Health Perspect.* 34: 165-183.
- Thomas, K. W.; Pellizzari, E. D.; Clayton, C. A.; Whitaker, D. A.; Shores, R. C.; Spengler, J.; Özkaynak, H.; Froehlich, S. E.; Wallace, L. A. (1993) Particle total exposure assessment methodology (PTEAM) 1990 study: method performance and data quality for personal, indoor, and outdoor monitoring. *J. Exposure Anal. Environ. Epidemiol.* 3: 203-226.
- Thomson, M.; Pillion, J. (1991) Children's respiratory hospitalizations and air pollution. *Can. J. Public Health* 82: 203-204.
- Thurston, G. D.; Kinney, P. L. (1995) Air pollution epidemiology: considerations in time-series modeling. In: Phalen, R. F.; Bates, D. V., eds. *Proceedings of the colloquium on particulate air pollution and human mortality and morbidity*; January 1994; Irvine, CA. *Inhalation Toxicol.* 7: 71-83.
- Thurston, G. D.; Özkaynak, H. (1992) Air pollution and mortality [letter]. *Science (Washington, DC)* 255: 382-383.
- Thurston, G. D.; Ito, K.; Lippmann, M.; Hayes, C. (1989) Reexamination of London, England, mortality in relation to exposure to acidic aerosols during 1963-1972 winters. In: *Symposium on the health effects of acid aerosols*; October 1987; Research Triangle Park, NC. *Environ. Health Perspect.* 79: 73-82.
- Thurston, G. D.; Ito, K.; Kinney, P. L.; Lippmann, M. (1992) A multi-year study of air pollution and respiratory hospital admissions in three New York State metropolitan areas: results for 1988 and 1989 summers. *J. Exposure Anal. Environ. Epidemiol.* 2: 429-450.

- Thurston, G. D.; Gorczynski, J. E., Jr.; Currie, J. H.; He, D.; Ito, K.; Hipfner, J.; Waldman, J.; Lioy, P. J.; Lippmann, M. (1994a) The nature and origins of acid summer haze air pollution in metropolitan Toronto, Ontario. *Environ. Res.* 65: 254-270.
- Thurston, G. D.; Ito, K.; Hayes, C. G.; Bates, D. V.; Lippmann, M. (1994b) Respiratory hospital admissions and summertime haze air pollution in Toronto, Ontario: consideration of the role of acid aerosols. *Environ. Res.* 65: 271-290.
- Touloumi, G.; Pocock, S. J.; Katsouyanni, K.; Trichopoulos, D. (1994) Short-term effects of air pollution on daily mortality in Athens: a time-series analysis. *Int. J. Epidemiol.* 23: 957-967.
- Tromp, S. W. (1980) *Biometeorology: the impact of weather and climate on humans and their environment (animals and plants)*. London, United Kingdom: Heyden.
- Tseng, R. Y. M.; Li, C. K.; Spinks, J. A. (1992) Particulate air pollution and hospitalization for asthma. *Ann. Allergy* 68: 425-432.
- Tzonou, A.; Maragoudakis, G.; Trichopoulos, D.; Zavitsanos, X.; Dimopoulou, I.; Toupadaki, N.; Kremastinou, J. (1992) Urban living, tobacco smoking, and chronic obstructive pulmonary disease: a study in Athens. *Epidemiology* 3: 57-60.
- U.S. Centers for Disease Control. (1994) Populations at risk from particulate air pollution—United States, 1992. *Morb. Mortal. Wkly. Rep.* 43: 290-293.
- U.S. Centers for Disease Control. (1995) Asthma—United States, 1982-1992. *Morb. Mortal. Wkly. Rep.* 43: 952-955.
- U.S. Department of Health, Education, and Welfare. (1964) *Smoking and health: report of the Advisory Committee to the Surgeon General of the Public Health Service*. Washington, DC: Public Health Service; p. 60.
- U.S. Environmental Protection Agency. (1982a) *Air quality criteria for particulate matter and sulfur oxides*. Research Triangle Park, NC: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; EPA report no. EPA-600/8-82-029aF-cF. 3v. Available from: NTIS, Springfield, VA; PB84-156777.
- U.S. Environmental Protection Agency. (1982b) *Review of the national ambient air quality standards for particulate matter: assessment of scientific and technical information*. Research Triangle Park, NC: Office of Air Quality Planning and Standards, Strategies and Air Standards Division; report no. EPA-450/5-82-001. Available from: NTIS, Springfield, VA; PB82-177874.
- U.S. Environmental Protection Agency. (1986a) *Second addendum to air quality criteria for particulate matter and sulfur oxides (1982): assessment of newly available health effects information*. Research Triangle Park, NC: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; EPA report no. EPA-600/8-86-020F. Available from: NTIS, Springfield, VA; PB87-176574.
- U.S. Environmental Protection Agency. (1986b) *Review of the national ambient air quality standards for particulate matter: updated assessment of scientific and technical information, addendum to the 1982 OAQPS staff paper*. Research Triangle Park, NC: Office of Air Quality Planning and Standards, Strategies and Air Standards Division; report no. EPA/450/05-86/012. Available from: NTIS, Springfield, VA; PB87-176871/XAB.
- U.S. Environmental Protection Agency. (1986c) *Air quality criteria for ozone and other photochemical oxidants*. Research Triangle Park, NC: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; EPA report nos. EPA-600/8-84-020aF-eF. 5v. Available from: NTIS, Springfield, VA; PB87-142949.

U.S. Environmental Protection Agency. (1989) An acid aerosols issue paper: health effects and aerometrics. Research Triangle Park, NC: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; EPA report no. EPA-600/8-88-005F. Available from: NTIS, Springfield, VA; PB91-125864.

- U.S. Environmental Protection Agency. (1992) Respiratory health effects of passive smoking: lung cancer and other disorders. Washington, DC: Office of Research and Development, Office of Health and Environmental Assessment; EPA report no. EPA/600/6-90/006F. Available from: NTIS, Springfield, VA; PB93-134419/XAB.
- U.S. Environmental Protection Agency. (1993) Air quality criteria for oxides of nitrogen. Research Triangle Park, NC: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; EPA report no. EPA/600/8-91/049aF-cF. 3v. Available from: NTIS, Springfield, VA; PB95-124533, PB95-124525, PB95-124517.
- U.S. Environmental Protection Agency. (1996) Air quality criteria for ozone and related photochemical oxidants [draft final]. Research Triangle Park, NC: National Center for Environmental Assessment-RTP Office; EPA report nos. EPA/600/AP-93/004aF-cF. 3v.
- U.S. Senate. (1968) Air quality criteria staff report. Washington, DC: Committee on Public Works; serial no. 94-411.
- Ulm, K. (1991) A statistical method for assessing a threshold in epidemiological studies. *Stat. Med.* 10: 341-349.
- United Kingdom Ministry of Health. (1954) Mortality and morbidity during the London fog of December 1952. London, United Kingdom: Her Majesty's Stationery Office. (Reports on public health and medical subjects no. 95).
- Utell, M. J.; Morrow, P. E.; Speers, D. M.; Darling, J.; Hyde, R. W. (1983) Airway responses to sulfate and sulfuric acid aerosols in asthmatics: an exposure-response relationship. *Am. Rev. Respir. Dis.* 128: 444-450.
- Vedal, S.; Schenker, M. B.; Samet, J. M.; Speizer, F. E. (1984) Risk factors for childhood respiratory disease: analysis of pulmonary function. *Am. Rev. Respir. Dis.* 130: 187-192.
- Waldron, H. A. (1974) The blood lead threshold. *Arch. Environ. Health* 29: 271-273.
- Waller, R. E. (1963) Acid droplets in town air. *Int. J. Air Water Pollut.* 7: 773-778.
- Waller, R. E. (1971) Air pollution and community health. *J. R. Coll. Physicians (London)* 5: 362-368.
- Waller, R. E.; Lawther, P. J. (1957) Further observations on London fog. *Br. Med. J.* 4: 1473-1475.
- Walters, S.; Griffiths, R. K.; Ayres, J. G. (1994) Temporal association between hospital admissions for asthma in Birmingham and ambient levels of sulphur dioxide and smoke. *Thorax* 49: 133-140.
- Wang, X.; Dockery, D. W.; Wypij, D.; Fay, M. E.; Ferris, B. G., Jr. (1993a) Pulmonary function between 6 and 18 years of age. *Pediatr. Pulmonol.* 15: 75-88.
- Wang, X.; Dockery, D. W.; Wypij, D.; Gold, D. R.; Speizer, F. E.; Ware, J. H.; Ferris, B. G., Jr. (1993b) Pulmonary function growth velocity in children 6 to 18 years of age. *Am. Rev. Respir. Dis.* 148: 1502-1508.
- Ware, J. H.; Thibodeau, L. A.; Speizer, F. E.; Colome, S.; Ferris, B. G., Jr. (1981) Assessment of the health effects of atmospheric sulfur oxides and particulate matter: evidence from observational studies. *Environ. Health Perspect.* 41: 255-276.
- Ware, J. H.; Ferris, B. G., Jr.; Dockery, D. W.; Spengler, J. D.; Stram, D. O.; Speizer, F. E. (1986) Effects of ambient sulfur oxides and suspended particles on respiratory health of preadolescent children. *Am. Rev. Respir. Dis.* 133: 834-842.
- Weiss, K. B. (1990) Seasonal trends in US asthma hospitalizations and mortality. *JAMA J. Am. Med. Assoc.* 263: 2323-2328.
- Weiss, S. M.; Hudson, L. D. (1994) Outcome from respiratory failure. *Crit. Care Clin.* 10: 197-215.

- Weitzman, M. (1986) School absence rates as outcome measures in studies of children with chronic illness. *J. Chronic Dis.* 39: 799-808.
- Weitzman, M.; Klerman, L. V.; Alpert, J. J.; Lamb, G. A.; Kayne, H.; Rose, L. (1986) Factors associated with excessive school absence. *Pediatrician* 13: 74-80.
- Wennberg, J. E. (1987) Population illness rates do not explain population hospitalization rates: a comment on Mark Blumberg's thesis that morbidity adjusters are needed to interpret small area variations. *Med. Care* 25: 354-359.
- Wennberg, J. E.; McPherson, K.; Caper, P. (1984) Will payment based on diagnosis-related groups control hospital costs? *N. Engl. J. Med.* 311: 295-300.
- Westfall, P. H.; Young, S. S. (1993) Resampling-based multiple testing: examples and methods for *p*-value adjustment. New York, NY: John Wiley & Sons, Inc.
- White, M. C.; Etzel, R. A.; Wilcox, W. D.; Lloyd, C. (1994) Exacerbations of childhood asthma and ozone pollution in Atlanta. *Environ. Res.* 65: 56-68.
- Whittemore, A. S.; Korn, E. L. (1980) Asthma and air pollution in the Los Angeles area. *Am. J. Public Health* 70: 687-696.
- Wichmann, H.-E.; Sugiri, D.; Islam, M. S.; Haake, D.; Roscovanu, A. (1988a) Lungenfunktion und Carboxyhämoglobin in der Smogsituation des Januar 1987 [Pulmonary function and carboxyhemoglobin during the smog episode in January 1987]. *Zentralbl. Bakteriol. Mikrobiol. Hyg. Abt. 1 Orig. B* 187: 31-43.
- Wichmann, H.-E.; Sugiri, D.; Herold, G.; Knülle, E. (1988b) Atemwiderstandsmessungen bei Gesunden im Winterhalbjahr 1985/86 und im Januar/Februar 1987 [Measurement of airway resistance in healthy persons during the winter of 1985/86 and in January and February 1987]. *Zentralbl. Bakteriol. Mikrobiol. Hyg. Ser. B* 185: 509-519.
- Wichmann, H. E.; Mueller, W.; Allhoff, P.; Beckmann, M.; Bocter, N.; Csicsaky, M. J.; Jung, M.; Molik, B.; Schoeneberg, G. (1989) Health effects during a smog episode in West Germany in 1985. In: Symposium on the health effects of acid aerosols; October 1987; Research Triangle Park, NC. *Environ. Health Perspect.* 79: 89-99.
- Williams, M. K. (1970) Sickness absence and ventilatory capacity of workers exposed to sulphuric acid mist. *Br. J. Ind. Med.* 27: 61-66.
- Wilson, W. E.; Suh, H. H. (1995) Differentiating fine and coarse particles: definitions and exposure relationships relevant to epidemiological studies. In: Schmidt-Ott, A., ed. Trends in aerosol research IV: new approaches in aerosol science and technology, proceedings of the seminar; January; Gerhard Mercator University, Duisburg, Germany. Duisburg, Germany: Gerhard Mercator University of Duisburg; pp. 57-71.
- Wolff, G. T.; Stroup, C. M.; Stroup, D. P. (1983) The coefficient of haze as a measure of particulate elemental carbon. *J. Air Pollut. Control Assoc.* 33: 746-750.
- World Health Organization. (1977) Manual of the international statistical classification of diseases, injuries, and causes of death. Geneva, Switzerland: World Health Organization.
- World Health Organization. (1996) Climate change and human health. Geneva, Switzerland: WHO/WMO/UNEP; in press.
- Wright, A. L.; Taussig, L. M.; Ray, C. G.; Harrison, H. R.; Holberg, C. J. (1989) The Tucson children's respiratory study: II. lower respiratory tract illness in the first year of life. *Am. J. Epidemiol.* 129: 1232-1246.
- Wyzga, R. (1978) The effect of air pollution upon mortality: a consideration of distributed lag models. *JASA J. Am. Stat. Assoc.* 73: 463-472.

- Wyzga, R. E.; Lipfert, F. W. (1995a) Ozone and daily mortality: the ramifications of uncertainties and interactions and some initial regression results. Presented at: AWMA specialty conference on tropospheric ozone; May 1994; Orlando, FL. Pittsburgh, PA: Air & Waste Management Association; in press.
- Wyzga, R. E.; Lipfert, F. W. (1995b) Temperature-pollution interactions with daily mortality in Philadelphia. In: Particulate matter: health and regulatory issues: proceedings of an international specialty conference; April; Pittsburgh, PA. Pittsburgh, PA: Air & Waste Management Association; pp. 3-42. (A&WMA publication VIP-49).
- Xu, Z.-Y.; Blot, W. J.; Xiao, H.-P.; Wu, A.; Feng, Y.-P.; Stone, B. J.; Sun, J.; Ershow, A. G.; Henderson, B. E.; Fraumeni, J. F., Jr. (1989) Smoking, air pollution, and the high rates of lung cancer in Shenyang, China. *J. Natl. Cancer Inst.* 81: 1800-1806.
- Xu, X.; Dockery, D. W.; Wang, L. (1991) Effects of air pollution on adult pulmonary function. *Arch. Environ. Health* 46: 198-206.
- Xu, X.; Gao, J.; Dockery, D. W.; Chen, Y. (1994) Air pollution and daily mortality in residential areas of Beijing, China. *Arch. Environ. Health* 49: 216-222.
- Yano, E.; Yokoyama, Y.; Higashi, H.; Nishii, S.; Maeda, K.; Koizumi, A. (1990) Health effects of volcanic ash: a repeat study. *Arch. Environ. Health* 45: 367-373.
- Zeger, S. L.; Liang, K.-Y. (1986) Longitudinal data analysis for discrete and continuous outcomes. *Biometrics* 42: 121-130.